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THE SYNDROME OF PAINFUL DISABILITY OF THE SHOULDER AND HAND COMPLICATING CORONARY OCCLUSION

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WE WISH to describe a syndrome of painful disability of both the shoulder and hand which persists for several months to one or two years after coronary occlusion. It seems clear that it is precipitated by coronary occlusion, inasmuch as only six of eighteen patients had had any previous upper extremity pain, and in these six the pain was markedly increased by the cardiac attack.

The syndrome of combined shoulder and hand disability has not been described, although we feel that it is not a rare sequel of coronary occlusion. Several cases in Ernstene's report[1] are, we believe, of this type. We do not refer to the left arm and hand pain after a paroxysm of angina pectoris, when the extremity is held immobile for fear of exciting more pain, but to a persistent, painful disability which is associated with restriction of shoulder movement and swelling of the fingers.

MATERIAL

We have observed twenty-two patients with this syndrome. The diagnosis of coronary occlusion was made in eighteen, and was confirmed by the electrocardiogram in fifteen. We have included four more with a diagnosis of long-standing angina pectoris. In all four there had been an unusually severe attack prior to the development of the shoulder and hand pain. Several of the eighteen had had repeated occlusions. There were eleven men and eleven women, ranging in age from 48 to 79.

THE SYNDROME

It is important to emphasize that the syndrome was coincident with, or occurred after, coronary occlusion or persistent angina pectoris; otherwise, it might be dismissed as a fortuitous event which was only to be expected in patients beyond the age of 40. Because of the rather uncertain

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nature of the whole symptom complex and its mechanism of production, we wish to describe the changes in detail.

The syndrome resembles that of acute or subacute periarthritis of one or both shoulders, followed, usually in days or weeks, by stiffness, pain, and swelling of one or both hands (Table I). The shoulder involvement is associated with painful restriction of arm abduction and external rotation.

The onset of the pain may coincide with the occlusion, and it may be of excruciating intensity, requiring morphine, with marked trapezial tenderness, or it may appear several weeks after the cardiac seizure, and be mild, localized to the deltoid area, and attributed, perhaps, to a hypodermic injection. In one case, the shoulder pain developed seven months after the occlusion. Those whose pain came weeks or months later usually first noticed distress on abduction, as in the act of putting on a coat. Either or both shoulders may be involved. This disability, which prevents abduction or external rotation, lasts, although gradually improving, for an average of six months. Within a few days or weeks, there appears a mild unilateral or bilateral pain in the hands, with stiffness and inability to close the hand. This stiffness grows quickly worse; the finger joints become swollen; and the skin becomes tense and glossy, with obliteration of the interphalangeal wrinkling. The hand, in severe cases, is fixed in extension. There is often a deep rose-red suffusion of the palms. Usually, there is pain only with an attempt to close the hand. The fingers are more stiff than painful. In one instance, however, there was exquisite tenderness of the hand, with constant burning pain which was made worse by heat and relieved by ice. A violaceous discoloration appeared on the palm, and both palm and dorsum developed an exfoliative rash.

In another case, that of a pediatrician, the appearance of the hands, with their swollen, tense joints, glossy skin, and purplish-red discoloration of the palms led the patient and a colleague to state "if these changes occurred in children, we would diagnose them as acrodynia."

These two cases suggested that the role of the sympathetic nerves was predominant. The more common type suggests merely a rather rapid development of arthritis, with a very gradual improvement.

The hand involvement subsequent to the shoulder pain is probably an extension of the syndrome of shoulder pain alone after coronary occlusion, as previously described.*[3, 4] A number of patients who were seen long after coronary occlusion and had had severe shoulder pain did not mention hand swelling and stiffness, but the fact that these symptoms occurred was elicited by questioning. I think that this occurs in many of those who supposedly have shoulder involvement alone, but is of minor degree and may be overlooked.

*The following report was not seen when this paper was written: Spillane, J. D., and White, Paul D.: Brit. Heart J. Atypical Pain in Angina Pectoris and Myocardial Infarction, April, 1940.

It is interesting that many patients, after a few months, develop distinct thickening of the palmar aponeurosis near the metacarpophalangeal junction, usually of the middle and ring fingers. The overlying skin is puckered and thick and resembles the early stage of Dupuytren's contracture. This was called to my attention by Dr. William Paul Thompson in two of his cases, and I have been able to find it in five others. The hardening fails to progress to contracture and has noticeably diminished in two cases. Its association with the syndrome seems to be definite and not fortuitous, although its significance is not clear.

The shoulder pain usually appeared first, but in five of twenty-two cases the hand pain preceded the shoulder pain by one to four months.

Both in the shoulder and hand the pain is relatively intractable and persists for months. Improvement is gradual; usually the shoulder pain leaves first, with slower improvement in the hand, in which the swelling and disability may completely or partially disappear. This may take months or one to two years. Of ten patients who were seen from fifteen months to two and a half years after occlusion (Table I), only two have completely recovered the function of their hands. In only two of twenty-two cases were joints other than the shoulders or hands involved after the occlusion. In one there was pain in the right hip, and, in the other, in both ankles.

A PAINFUL POINT

During the stage of shoulder pain, a point of localized tenderness was found in fifteen of sixteen cases in which pressure was exerted over the anterior border of the trapezius muscle upon the mesial angle of the superior border of the scapula. The more severe the shoulder pain, the more acutely tender was this point. It apparently corresponded to the site of trapezius branches of the cervical plexus. The brachial plexus was not acutely sensitive to pressure.

Libman, et al.,[2] have reported that the pain of subacromial bursitis may be relieved by pressure against the spine at the level of the angle of the jaw. In certain cases, Boas and Levy[3] were able to relieve the shoulder pain which followed coronary occlusion by pressure on the brachial plexus. Edeiken and Wolferth[4] described a "trigger zone over the upper border of the left scapula where pressure induced pain in the left shoulder and up over the left side of the neck."

In two cases in which shoulder pain developed simultaneously with the occlusion, we decided to attempt to relieve it by pressing over the painful trapezius. Pressure caused such agonizing pain that it could be applied only after the administration of evipal. Then it was applied over the painful point for three minutes. The relief of pain and limitation of motion were remarkable. In one case the relief was permanent; in the other the pain has returned on several occasions after overwork, and each time it has been relieved by pressure. In a third case, in which

TABLE I

ANALYSIS OF TWENTY-TWO CASES OF SHOULDER AND HAND DISABILITY COMPLICATING CORONARY ARTERY DISEASE

AGE	SEX	TIME BETWEEN OCCLUSION AND SHOULDER PAIN	TIME BETWEEN SHOULDER PAIN AND HAND PAIN	DURATION OF SHOULDER PAIN	DURATION OF HAND PAIN	ROENTGENOGRAPHIC CHANGES	PRESENT STATUS	TIME AFTER OCCLUSION
60	F	1 week	3 weeks	6 months	3 months	Osteoarthrosis both acromioclavicular joints; demineralization both hands	Patient is at work as buyer; has return of shoulder pain when overworking, and is relieved by pressure over trapezius	2½ years
68	F	2 days	4 weeks	9 months	16 months	Osteoarthrosis both acromioclavicular joints; both hands, advanced atrophic arthritis	Hands now can be nearly closed and are not painful. No return of shoulder pain	2 years
63	F	Immediate	Immediate	11 months	2 years	Osteoarthrosis right acromioclavicular joint and both hands	Right hand still cannot be closed	2½ years
63	M	3 months	3 weeks	6 months	6 months	Osteoarthrosis both acromioclavicular joints; both hands normal	No further shoulder or hand pain. Is back at work as steam engineer	15 months
47	M	Immediate	4 weeks	6 months	6 months	Roughened tuberosity both shoulders; no hand changes	Back at work as baker. No return of pain	1½ years
51	M	*	*	12 months	18 months	Calcified bursa right shculder; no other roentgenograms made	Still some hand swelling and pain. Shoulder pain improved	2 years
48	F	2 months	Simultaneous	18 months	18 months	Demineralization left humerus, left hand	Still restriction of shoulder and hands, but much improved	2 years
57	M	6 weeks	4 weeks	18 months	22 months plus	Shoulders normal; both hands early atrophic arthritis	Hands slightly swollen, stiff and painful. Shoulder pain gone	2 years
54	M	4 weeks	1 week	1½ years	1½ years	No roentgenograms made	Died of second coronary thrombosis 1½ years after first	
62	M	3 months	1 week	4 months plus	4 months plus	Calcified bursa right shoulder; sharpened margins both hands	Not located	

74	F	6 months	Coincident	6 months	6 months	Osteoarthrosis both shoulders; moderate atrophic arthritis both hands	Not located	2 years
64	M	2 days	2 weeks	7 months	7 months	Right shoulder normal; no other roentgenograms made	Died of congestive heart failure 8 months after occlusion	
71	F	3 days	2 weeks	6 months	6 months	Osteoarthrosis both shoulders, both hands	Shoulder pain gone. Right hand shows slight thickening of palmar fascia. Some stiffness	16 months
48	M	*	*	6 months	8 months	Shoulders normal; both hands early atrophic arthritis	Definite hardening of right palmar fascia. Stiffness of hands	16 months
71	M	7 months	5 weeks	2 months plus	2 months plus	Roughtened tuberosity left humerus; no hand changes	Not located	
54	M	*	*	2 months	6 months	Acromioclavicular roughening; both hands early atrophic arthritis	Disability gone in both shoulders and hands	1 year
79	F	5 days	3 weeks	1 month	6 months plus	Shoulders normal; osteoarthrosis both hands	Right hand cannot be closed. Shoulder pain gone. Thickening of palmar fascia	6 months
64	M	8 months constant angina	4 months	6 months	6 weeks	No abnormalities	Shoulder pain relieved surgically. Right hand still slightly stiff. Thickening of palmar fascia	6 months
66	F	5 years angina pectoris	2 weeks	6 months plus	6 months plus	Osteoarthrosis right shoulder and hand	Still disabled with shoulder and hand. Left palmar fascia thickening	6 months
59	F	10 years angina pectoris	*	1 month	2 months plus	No shoulder changes. Both hands, osteoarthrosis	Shoulder pain gone. Hands stiff	1 month
47	F	6 weeks	1 week	4 months plus	4 months plus	Normal	Shoulder pain present. Both hands stiff. Slight thickening right palmar fascia	4 months
53	F	8 years angina	*	3 months plus	2 months	Normal	Hands can be closed. Right palmar fascia thickened and hard	6 months

*Hand pain preceded shoulder pain.

pressure was applied one month after the development of the shoulder pain, there was partial relief.

In another case of pain in the shoulder of many months' duration, pressure gave no relief from the pain caused by abduction.

As most of the patients were seen a number of months after the onset of shoulder pain, when they had established disability of the shoulder and swelling of the hands, pressure was not attempted, although increased tenderness was found in all but one case. Hypersensitive persons are somewhat tender over this point, and it is important to disregard anything but marked tenderness.

It may be significant that, in this atypical syndrome with shoulder pain, the cervical plexus nerves are sensitive. We have not found this marked sensitivity in cases of coronary occlusion without shoulder pain. Edeiken and Wolferth's[4] trigger zones over the scapula, which are associated with postocclusion shoulder pain, may also represent sensitized cervical plexus nerves. The significance of this observation is uncertain. We mention it merely so that it may be studied by others. The relief of the acute, excruciating pain in two cases was dramatic, but the explanation is obscure. We do not feel that the evipal was a factor.

LOCALIZATION OF JOINT INVOLVEMENT

Persistent pain and disability developed predominantly in the left shoulder and left hand in ten cases, in the right shoulder and hand in eleven cases, and in one there was no difference, i.e., both shoulders and both hands were equally involved. This high percentage of patients with right-sided involvement, which is contrary to the typical left-sided anginal radiation, suggested the possibility of pre-existing arthritis as an etiological factor. The occurrence of pain and swelling in the hand preceding the shoulder involvement in five cases was an additional feature. The role of coronary occlusion in precipitating the syndrome seemed definite.

PRE-EXISTING ARTHRITIS

Whether or not there was a pre-existing arthritis must be ascertained from the history and the interpretation of the roentgenograms. Five patients gave a history of previous pain in the shoulder, and in all of these cases it was mild. One gave a history of preceding hand involvement. She had had stiffness of the hands since undergoing a thyroidectomy eight years before. Of two others, one had had rheumatic fever at the age of 15 years, and the other had had mild osteoarthritis of both knees several years before. Fourteen gave no history of any previous joint trouble.

ROENTGENOLOGIC OBSERVATIONS

Roentgenograms were taken of both shoulders and both hands in nineteen cases, regardless of the site of the pain and disability. The discordance between clinical signs and symptoms and roentgenologic interpretations in the case of any one joint is well known.

Roentgenograms of both shoulders and both hands were made in nineteen cases; in sixteen of these cases there were bony changes in either the shoulders or hands. Several roentgenologists were asked to interpret the abnormalities, and their individual opinions concurred. Two other patients had single roentgenograms of the affected shoulder; one showed a calcific bursitis, and the other showed no change. In one case no roentgenologic examination was made. There was no absolute correlation between the degree of change and the side of greater involvement. Of the nine patients with predominantly left-sided pain, six had bilaterally equal or chiefly left-sided roentgenographic changes. Two showed more abnormalities on the right side than on the left.

Those with predominantly right-sided involvement showed, usually, roentgenologic changes in both shoulders.

The natural tendency for anginal radiation to be left sided makes any correlation difficult.

TREATMENT

Various measures were used in the treatment, and were directed chiefly at the relief of pain. Aside from the narcotics, they seemed of little value. Cobra venom, bee venom, large doses of thiamin, salicylates, and, in one case, a paravertebral alcohol injection of the first and second dorsal sympathetic ganglia had only a negligible effect. The patients who had foci of infection removed did no better than the others. In many cases, heat was intolerable in the early stages, but later, with massage, seemed to help the hands.

DISCUSSION

The important point in this syndrome, in my opinion, is the precipitating effect of coronary occlusion. Although the syndrome occurred in four cases in which only severe angina pectoris was diagnosed, there is a strong suspicion that unrecognized occlusion may have occurred.

The sequence of events seemed to be myocardial ischemia, cardiac pain, shoulder pain, and, later, hand pain.

Clinically, the manifestations in the hand were caused by a combination of sympathetic nerve disturbance and arthritis, with varying degrees of predominance of one or the other. With causalgia as a result of sympathetic nerve irritation, the skin of the hands becomes smooth, glossy, and bright red; this occurred in a number of our cases. Dupuytren's contracture is regarded by many neurologists as the result of dysfunction of the sympathetic nervous system.[7] It was found in seven of ten of our patients who were examined for it.

The course of the hand disability, although it persisted in many cases for two years, was characteristic of neither long-standing rheumatoid arthritis nor osteoarthritis. The hands lacked the muscle atrophy of the former and the Herberden's nodes of the latter, and they gradually improved rather than becoming worse.

The shoulder pain was similar to that which occurs with periarthritis. Ordinary periarthritis is usually ascribed to trauma, infection, or a metabolic disturbance. Trauma and infection can be eliminated as precipitating factors following coronary occlusion. That the action of coronary occlusion in causing shoulder pain is causalgic has been suggested by Edeiken and Wolferth. The possibility of an accompanying cervical neuralgia was suggested in our cases by the apparent sensitization of cervical plexus nerves and by the relief that some of the patients obtained from pressure.

Miller[6] has demonstrated accessory nerve pathways which may connect afferent pain stimuli from the heart and from the shoulder. We feel this can explain the mechanism of production of the syndrome. Afferent impulses from the shoulder enter the fourth, fifth, and sixth cervical ganglia. Accessory sympathetic cardiac afferent fibers may also enter at this level. This would explain the sensitiveness of the trapezius, which is innervated by the cervical plexus.

The significance of localized lesions in determining the radiation of cardiac pain stimuli has been emphasized by Boas and Levy.[3] We feel that the difference in the syndromes, after coronary occlusion, of shoulder pain without restriction of movement, shoulder pain with restriction of movement, and shoulder pain plus hand involvement is probably one of degree and depends upon several factors.

The intensity of the cardiac afferent stimulus, the degree of joint involvement, and the sensitivity of the patient are probably determining factors.

It is difficult to say what the mechanism is, but the following deductions seem justifiable:

1. The painful shoulder and hand syndrome herein described is clearly a sequel of coronary occlusion. When it appears in connection with repeated attacks of angina pectoris, we believe that a "silent" occlusion should be suspected.

2. Latent arthritic changes are usually present in the shoulder and hand.

3. The process is self-limited and seems to be little affected by any type of therapy. Infection apparently plays a negligible role.

4. The syndrome seems to be the resultant of sympathetic nerve disturbance caused by myocardial ischemia and pre-existing shoulder and hand lesions.

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DISCUSSION

DR. EMANUEL LIBMAN, New York.—This elaborate and well-prepared presentation of Dr. Askey's is a very welcome contribution. It is of particular interest to me, because in the interpretation which I will place upon it, and which, as he has intimated, he believes to be correct, it points again to what I have long believed to be the essential etiological factor in coronary artery disease and coronary thrombosis, namely, a diathetic metabolic disturbance, called the "gouty" state. This term is used to indicate a disorder of which we have no really definite knowledge, except that it is caused by hepatic dysfunction. The idea that a change in uric acid metabolism is the primary cause of "gout" or "goutiness" (atypical gout) is not now accepted by many clinical investigators. Some time ago I put forth the suggestion that an essential element is an abnormality of lipoid metabolism and that the uric acid disturbance probably arises secondarily. Interesting and important in this connection are publications during the last few years in which it was demonstrated that, in cases in which there had been typical attacks of "gout," the administration of a high-fat diet would bring on such attacks and that they were accompanied by an elevation of the uric acid content of the blood.

Dr. Askey has spoken of three possible explanations of the clinical picture to which his paper is devoted: (1) that it is entirely dependent upon the coronary thrombosis, (2) that it is the result of a metabolic disturbance, and (3) that it is caused by a combination of the first two mechanisms.

What evidence have we in favor of the possibility that the condition is of metabolic origin and not entirely dependent upon the state of the myocardium? Strong evidence is afforded by observations on patients who have suffered coronary occlusion with the pain limited entirely to the left side and then develop a shoulder disorder on the right side. Further evidence of the role of a metabolic disturbance was presented in two of the cases described today, in which there were symptoms in the right hip and right ankle.

The occurrence of Dupuytren's contraction, in my opinion, also points to a metabolic disturbance. In several cases of Dupuytren's contraction in "gouty" persons, I have been able to study the mechanism of its development. In these cases I found that the first thing to appear was fine nodules, such as one finds elsewhere in "gout," in the tendons. These gradually increased; fibrous tissue developed between them; and then the tendons became attached to the skin. Apparently, the development of this fibrous tissue is increased by movement of the tendons. I cannot exclude a partial role on the part of the nervous system. If you will study your own hands and other parts of the body (especially the upper parts of the legs)—I am referring to those over 40 years of age—you will find such nodules in the tendons, fascia, and periosteum. Some are loose and later may become attached.

The cases of coronary artery atherosclerosis and coronary thrombosis must be studied from another standpoint. One must investigate the frequency in the patients' histories of the occurrence of hemorrhoids, bursitis, furuncles, carbuncles, pruritis (especially pruritis ani), and a number of other features of the "gouty diathesis." Careful statistical study is essential because these conditions are rather common.

We know that directly after coronary occlusion there may be certain phenomena as a result of the myocardial necrosis. Such necrosis may cause fever, leucocytosis, temporary joint inflammation, and mild jaundice. In relation to Dr. Askey's studies, however, I wish to draw attention to the possibility of effects produced by myocardial ischemia as such. It is not generally realized that the myocardial ischemia can influence the autonomic nervous system and activate conditions that may have already existed, or to which a tendency was already present.

We have a hint of this in the occurrence of pyloric spasm with eructation, and other discomforts, in patients suffering from the results of coronary artery disease. Here we may find evidence of what I have called "rebounds in the autonomic nervous system." If the heart is under strain, whether because of fresh coronary occlusion or insufficiency resulting from coronary narrowing, many conditions may occur, for example, pylorospasm and cardiospasm. As a result there may be eructation, with relief from the cardiac pain. I am not at all convinced that this is simply the result of a release from "pressure of the gas on the heart." I am inclined to believe that relief of the secondary spasm or spasms improves the condition of the heart by improving the circulation or by bringing about a diminution in tonicity. I could cite many examples of such "rebounds."

I have not found it necessary to use any anesthetic or sedative in carrying out the manipulation for relieving shoulder pains. If one explains to the patient that the method is painful, that he will probably be very uncomfortable, but that it may be of use, he will practically always allow one to finish the treatment. If necessary, one can, by pressing on one of his own Erb's points, show that it is painful to everyone.

DR. ERNST P. BOAS, New York.—This most interesting presentation of Dr. Askey's is important because physicians are still not recognizing this syndrome. I can confirm all of the clinical observations made by Dr. Askey. I too have seen these palmar contractures. I have seen a number of cases in which the acute shoulder syndrome antedated the coronary occlusion, and others, as he pointed out, in which a diagnosis of coronary occlusion was made because of the sudden appearance of the shoulder pain.

The problem of the mechanism and cause of this shoulder condition is a most interesting one, and I am inclined to agree that there must be an underlying local predisposition; whether it is a diathesis in the sense meant by Dr. Libman or whether it is simply a local disturbance I do not know.

In my personal experience, the involved shoulder usually was the shoulder to which there was radiation of the anginal pain. I have seen exceptions, but the discrepancies were by no means as great as those observed by Dr. Askey.

I have seen a few cases in which this shoulder syndrome appeared after other types of cardiac attacks. I had two patients with paroxysmal auricular fibrillation and some with aortic stenosis who developed this shoulder syndrome.

Whether the trophic disturbances in the hand can be attributed to reflex involvement of the sympathetic nervous system as a result of the cardiac lesion, I do not know. After all, similar disturbances occur in the hand following periarthritis of the shoulder which has no relationship to heart disease. On the other hand, there are many features of this clinical picture which suggest a mechanism analogous to causalgia.

Some of the other symptoms of which patients with coronary disease complain, namely, the marked muscular weakness of the left arm, trophic disturbances, perhaps in the absence of shoulder pain, herpes zoster in the distribution of the anginal pain, the response to pressure on the nerves of the brachial plexus or of the cervical nerves, as pointed out originally by Dr. Libman, suggest that there is most probably a causalgia-like mechanism underlying these clinical manifestations.

For the present I think we must predicate that there are two factors involved. One is the local condition of the shoulder, and the other is the reflex mechanism initiated by the afferent bombardment of stimuli from the heart. Beyond that I fear we cannot go. But it is most important to recognize and to evaluate this syndrome which has been so well delineated by Dr. Askey.

DR. H. R. MILLER, New York.—Perhaps it is feasible to look upon the anginal pain which is referred to the shoulder, or to any other atypical area, for that matter, as a manifestation registered in an unusual dermatomic segment.

Dr. Askey's cases leave little room for doubt that the disturbance he describes is related to a disease or derangement of the cardiovascular apparatus. The onset was definitely associated with coronary occlusion; there is, therefore, sound reason to believe that his premise that the shoulder pain is not a mere coincidence is correct. When the heart is already compromised for one reason or another, and pain is registered in an abnormal zone, we can account for the location of the pain only on the probability of transmission of pain impulses along afferent fiber tracts which are not commonly involved.

In Dr. Askey's cases, it seems to me, the evidence is clear—one might even say that it permits of no other interpretation—that there is a participation of accessory cervical branches of the afferent fiber system.

From the shoulder region afferent somatic nerves make their entry into C 4, 5, and 6 cord levels. The cardiac impulses, on the other hand, are carried by the upper four thoracic and eighth cervical nerves to corresponding cord levels. Between these two regions of entry lie several cord segments.

The shoulder region can be brought into relation to the cardiac plexuses when impulses from the latter arrive either (1) at the C 4-6 cervical cord levels through the intervention of accessory sympathetic neurons, or (2) at the upper thoracic cord levels where accessory somatic cervical fibers from the shoulder have found an entry.

With regard to pain initiated in the shoulder and reflected into the cardiac region or precordium, this eventuality is perhaps better understood if one realizes that any extracardiac territory or organ in the body may precipitate the so-called anginal syndrome. In this respect, a diseased gall bladder is not rare, but herniation of the esophagus or a painful bursa or shoulder are equivalent loci.

The effect achieved by the impulses which reach the cord segments for the mediation of pain is probably the result of a summation of impulses, in this case from the shoulder and from the cardiac plexuses. For the purpose of discussion we may designate the stream of afferent extracardiac impulses as (a), and those originating in the cardiac apparatus as (b). Sometimes the extracardiac territory, as in the case of the severe kind of neuritis described by Lian and his pupil Boyer, is sufficient to set off the "explosion." The patient looks as if he were in the throes of an attack of coronary occlusion, whereas, in reality, he has engendered an overwhelming number of (a) impulses. In most cases the heart itself gives rise to a quantity of impulses sufficient to produce anginal pain. Arthritis or any other localized pathologic condition of the shoulder which was pre-existent or developed after a coronary occlusion would make it possible for impulses of pain to be transmitted from the heart or shoulder into "overlapping" cord segments.

DR. LIBMAN.—I should like to add a word concerning the pigmentation of which Dr. Askey spoke. How often did you note the pigmentation?

DR. ASKEY.—That was the only instance.

DR. LIBMAN.—Because of the reference which was made to the question of involvement of the autonomic nervous system in these cases, I should like to draw attention to the fact that such involvement is present in a variety of joint affections.

You will find it very well described in the small monograph published long ago (1889) by Spender. He described the early clinical manifestations of what he called osteoarthritis, by which he meant rheumatoid arthritis, and pointed out that not infrequently, before the patients develop the joint disturbance, sweating, burning, tachycardia, pigmentation, and a variety of other symptoms may be present. I originally learned of Spender's work from Dr. Osler's *Practice of Medicine*. You will find a reference to it in the earlier editions.

DR. ASKEY.—It was a privilege to have these three men discuss my paper.

It was Boas and Levy's article in the AMERICAN HEART JOURNAL several years ago, which I read at a time when I had my first puzzling case, that aroused by interest in this subject. Dr Libman has been stimulating since the time when he pointed out that pressure over the acromial nerves would relieve the pain of subacromial bursitis. I asked him why he hadn't published this observation, and he said that he did not know why it relieved the pain and that he did not want to get a lot of letters about it. His concept that there is a gouty diathesis, in the sense of a lipoid disturbance rather than a uric acid disturbance, is, I feel, correct. Several of my patients showed some roentgenographic changes in the hands which were suggestive of gout; but there were no other findings, and the blood uric acid was normal.

Dr. Miller's discussion of the nerve pathways which are concerned when shoulder pain occurs with coronary occlusion was especially helpful to me.

THE PHYSIOLOGIC ACTION OF OXYGEN AND CARBON DIOXIDE ON THE CORONARY CIRCULATION, AS SHOWN BY BLOOD GAS AND ELECTROCARDIOGRAPHIC STUDIES

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THE effect of inhaling a mixture containing 12 per cent oxygen for twenty minutes is rarely noticed by most normal persons. Slight headache, vertigo, and a feeling of breathlessness may be experienced. The heart rate is increased, and the circulation time is shortened. In cases in which there is some impairment of the coronary circulation as a result of arteriosclerosis or narrowing of the mouths of the coronary arteries, the inhalation of low-oxygen mixtures frequently results in a profound disturbance of cardiac function. Precordial pain may occur,[1] and, at times, collapse, pulmonary edema, or shock; the arterial blood shows a diminished oxygen saturation, a decrease in carbon dioxide content, and a slight shift in pH toward the alkaline side.[2, 3] The heart rate is generally elevated, with a more marked increase in pulmonary ventilation[2] and decrease in circulation time[3] than takes place in normal subjects.

The electrocardiographic response to the inhalation of low-oxygen mixtures is generally less marked in normal subjects than in patients with coronary disease; lowering of the T wave and depression of the S-T segment are the characteristic changes.[2-6]

The inhalation of high-oxygen atmospheres has a physiologic action that is, in many instances, opposite to that of low-oxygen atmospheres. Thus, the precordial pain of coronary thrombosis can be relieved by the inhalation of a 50 per cent oxygen mixture,[7] and recently was relieved in a more striking manner by the inhalation of pure oxygen.[8] Patients with numerous seizures of anginal pain which persisted when they were at rest in bed became largely free from attacks after they were placed in an oxygen chamber.[9] Furthermore, when acute coronary occlusion is followed by peripheral circulatory failure, the inhalation of a 50 per cent oxygen mixture has been shown to relieve these symptoms in some cases.[10]

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The electrocardiographic effects of the inhalation of pure oxygen have recently been studied by the authors.[11] Normal persons generally showed no change; in a few subjects an increase in the height of the T wave was produced. In patients with coronary disease, however, the T wave frequently becomes elevated, and, when it was previously diphasic or depressed, the inhalation of pure oxygen frequently makes it upright or higher. These changes will be reported in full later in this article. The heart rate is decreased 4 to 6 beats per minute in most normal subjects by the inhalation of pure oxygen.

In summary, a diminished tension of oxygen in the arterial blood decisively impairs the function of the coronary circulation in patients with coronary disease; conversely, an increased tension of oxygen in the arterial blood improves the function of the coronary circulation when it has been previously damaged. In this investigation, the role of carbon dioxide in the regulation of the coronary circulation was studied by administering various combinations of oxygen and carbon dioxide, and by observing the blood gases, the pH, and the electrocardiographic response.

METHODS

The blood gas analyses and calculations of the pH were done by the method of Van Slyke and Neill.[12] The pulmonary ventilation was graphically recorded on a Tissot apparatus. The method of providing continuous inhalation of a constant gas mixture has been previously described.[3]

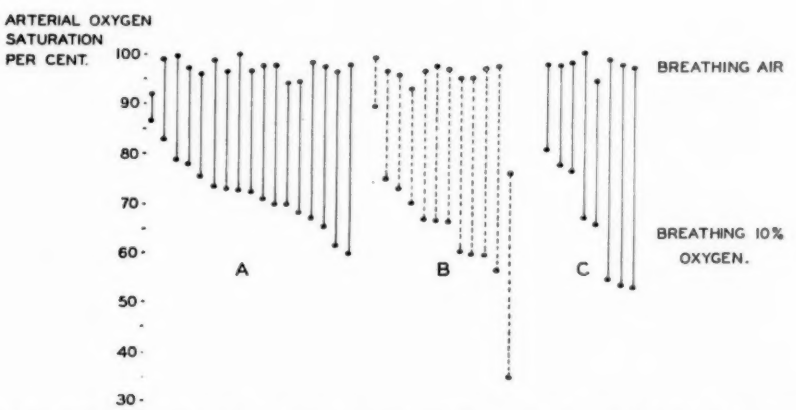

Chart I.—Fall in arterial oxygen saturation, induced by inhaling a 10 per cent oxygen atmosphere, in twenty-nine patients with heart disease and in eight normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individuals. Each line represents one person.

RESULTS

The degree of arterial anoxemia which was produced in twenty-nine patients with heart disease and eight normal subjects as a result of inhaling a 10 per cent oxygen mixture for approximately twenty minutes

is shown in Chart I. There were nine cases of hypertensive vascular disease and twenty cases of coronary disease. The arterial oxygen saturation varied from 57 to 88 per cent, except in one case in which the unaccountably low figure of 35 per cent was encountered. In seventeen of twenty-nine patients in the cardiac group, precordial pain was produced by inhaling the 10 per cent oxygen mixture. The inhalation of the low oxygen mixture was stopped at the time the pain occurred, and, therefore, these patients breathed the mixture for a shorter period than those who did not experience pain. No significant difference in the degree of arterial anoxemia could be observed between these two groups, or between the cardiac and the normal group.

The effect of inhaling a 10 per cent oxygen mixture on the carbon dioxide content of arterial blood is shown in Chart II. A decrease in the arterial carbon dioxide content of approximately 2 to 5 volumes per cent took place in twenty-four patients with heart disease, thirteen of whom developed pain during the test, and in five normal subjects.

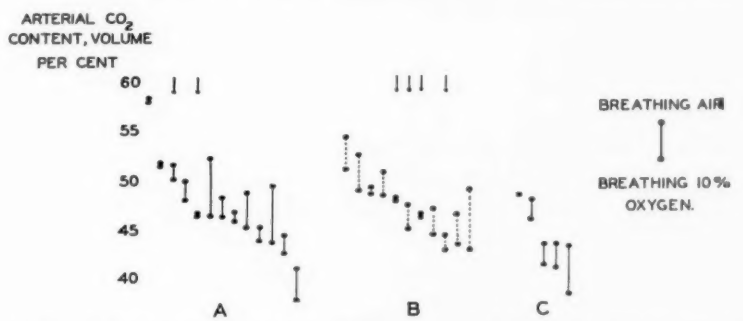

Chart II.—Fall in arterial carbon dioxide content induced by inhaling a 10 per cent oxygen atmosphere in twenty-four patients with heart disease and in five normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individuals. Each line represents one individual. Arrows indicate cases in which the arterial CO_2 rose when 10 per cent oxygen was inhaled.

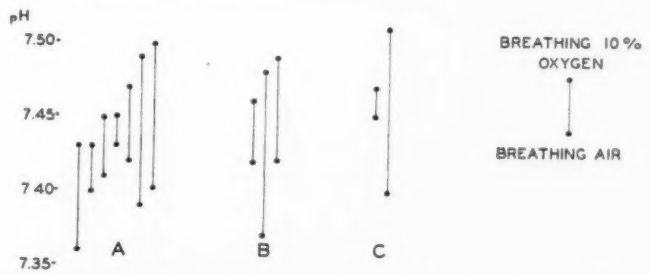

Chart III.—Rise in pH induced by inhaling a 10 per cent oxygen atmosphere, in ten patients with heart disease and in two normal subjects. *A*, Patients in whom cardiac pain was induced by inhaling the 10 per cent oxygen mixture. *B*, Patients in whom no cardiac pain was induced. *C*, Normal individual. Each line represents one person.

The pH of the arterial blood was ascertained in ten patients with heart disease and two normal subjects after the inhalation of a 10 per

cent oxygen mixture; the results are shown in Chart III. In seven cases precordial pain was initiated. The pH rose from 0.02 to 0.10; no difference was apparent between the two cardiac groups, or between the cardiac and the normal groups, but the series was admittedly small. It was apparent that overventilation due to acute anoxia lowered the free carbon dioxide of the blood to a greater degree than the combined carbon dioxide content, with a resultant increase in the alkalinity of the blood.

Electrocardiograms were taken of these patients before and at the conclusion of the period during which they inhaled the low oxygen mixture; no correlation between the degree of electrocardiographic change and the alteration in blood gas or pH equilibrium was observed.

The degree of alkaline shift in pH was in some cases so impressive as to suggest that alkalosis might play a role in the production of both the symptoms and the electrocardiographic changes of induced oxygen want. It is well known that alkalosis increases muscle and nerve irritability, at times to the point of tetany. Constriction of the capillary bed has been produced as a result of acute alkalosis, and, contrariwise, carbon dioxide administration has been followed by dilatation of these vessels.[13-16] Direct observation of the pial vessels by Wolff and Lennox[17] revealed that experimental alkalosis caused constriction, and acidosis produced by the inhalation of carbon dioxide resulted in dilatation of these vessels. The possibility presented itself that the coronary circulation would be affected in a similar way. It is interesting to note that petit mal attacks may be precipitated by inhaling low-oxygen mixtures, or by alkalosis produced by hyperventilation, and, conversely, that attacks of petit mal may be inhibited both by acidosis and increased oxygen tensions.[18, 19] A further similarity between the effect of anoxia and alkalosis should be mentioned, namely, that not only is the T wave lowered by induced anoxemia, but also, to a very slight extent, by induced alkalosis.[20]

The problem thus presented itself: Is the alkalosis that results from anoxia alone responsible either for spastic contraction of the coronary arteries or for constriction of the capillary bed? A new series of patients with heart disease and a group of normal subjects were then subjected to the induced anoxemia test, with and without the addition of small percentages of carbon dioxide. The presence of carbon dioxide in the low-oxygen mixture additionally stimulated respiration, and thereby produced a higher saturation of the arterial blood with oxygen than occurred when the low-oxygen atmosphere itself was breathed. In some cases, therefore, the effect of a 12 per cent oxygen atmosphere was compared to that of a 10 per cent oxygen and 3 per cent carbon dioxide mixture, and also a 10 per cent low-oxygen atmosphere to that of a 9 per cent oxygen with 2 or 3 per cent carbon dioxide mixture.

In Table I the electrocardiographic observations during inhalation of low-oxygen mixtures with and without the addition of carbon dioxide are summarized. Twenty-six tests were made on ten patients with heart disease, nine of whom were classified as having coronary sclerosis, two patients with miscellaneous disease, and eight normal subjects. The inhalation of a 10 to 12 per cent oxygen mixture in seven tests in the patient group resulted in significant changes in the electrocardiogram, such as lowering or inversion of the T wave or depression of the S-T segment. These changes, however, completely disappeared or were materially reduced when the same or a lower oxygen percentage was combined with 2 or 3 per cent carbon dioxide. In three patients no definite change took place with induced anoxemia, with or without carbon dioxide. In two patients the lowering of the T wave was slightly less marked during the inhalation of oxygen alone than when carbon dioxide was added, but in each instance the percentage of oxygen was lower when carbon dioxide was added. In six tests on normal subjects a definite lowering of the T wave was observed during inhalation of the low-oxygen mixture for a twenty-minute period; when 3 per cent carbon dioxide was added to the 10 per cent oxygen mixture, the T wave was normal. In tests on two additional normal persons there was no change either after inhalation of a 10 per cent oxygen mixture or a 10 per cent oxygen plus 3 per cent carbon dioxide mixture. The electrocardiographic changes induced by inhaling a mixture containing 10 per cent oxygen, and the effect of the addition of 3 per cent carbon dioxide on these changes are illustrated in Fig. 1.

In one case of coronary sclerosis, shock was induced by breathing a 10 per cent oxygen mixture for ten minutes; in four others precordial pain or distress was produced in a period of five to twenty minutes. In these five cases, inhalation of the same or lower concentrations of oxygen with 2 or 3 per cent carbon dioxide produced no symptoms whatsoever.*

In most cases of coronary disease, therefore, the addition of small percentages of carbon dioxide prevented or decreased the electrocardiographic effects of induced anoxemia. Before the results are interpreted, the blood gas analyses on some of these patients may be inspected. The blood was drawn after the electrocardiogram was taken, at the end of twenty minutes, unless pain occurred prior to that time. The data, which are shown in Table II, require detailed analysis.

In Case 1, the inhalation of a 9.3 per cent oxygen with 2 per cent carbon dioxide mixture resulted in an arterial oxygen saturation of 77.7 per cent, as compared to 68.5 per cent after the inhalation of a 10 per cent oxygen mixture without carbon dioxide; the pH was 7.46 after inhalation of the low-oxygen carbon dioxide mixture, and 7.52 after the low-oxygen mixture without carbon dioxide. Precordial distress

*The marked increase in ventilation was itself burdensome in the majority of cases.

TABLE I

ELECTROCARDIOGRAPHIC CHANGES DURING THE INHALATION OF 9 TO 12 PER CENT OXYGEN MIXTURES, WITH AND WITHOUT 2 TO 3 PER CENT CARBON DIOXIDE, IN CASES OF HEART DISEASE AND NEPHRITIS, AND NORMAL SUBJECTS

CASE NO.	DIAGNOSIS	DATE OF OBSERVATION (1940)	GAS MIXTURE BREATHED	ELECTROCARDIOGRAPHIC CHANGES	REMARKS
1	Coronary sclerosis	March 12	10% oxygen	T_1, T_4 inverted; S-T_2, S-T_3 depressed	Precordial distress
			10% oxygen, 3% carbon dioxide	T_1, T_4 upright; S-T_2, S-T_3 not depressed	No distress
		April 1	10% oxygen	T_4 inverted; T_1 diphasic; S-T_2, S-T_3 depressed	Precordial distress
			9.3% oxygen, 2% carbon dioxide	T_1, T_4 upright; S-T_2, S-T_3 not depressed	No distress
2	Coronary sclerosis and hypertensive vascular disease	March 15	10% oxygen	T_3 inverted; S-T_4 markedly depressed	
			10% oxygen, 3% carbon dioxide	T_3 upright; S-T_4 much less depressed	
		March 20	12% oxygen	S-T_2, S-T_3, S-T_4 depressed; T_3 lowered	
			10% oxygen, 2% carbon dioxide	S-T_2 not depressed; S-T_3, S-T_4 much less depressed	
3	Coronary sclerosis	March 16	10% oxygen	T_4 diphasic; T_1 lowered	After 10 minutes pulse and blood pressure fell; patient went into shock
			10% oxygen, 3% carbon dioxide	T_4 upright; T_1 higher	Breathed this mixture for 20 minutes without symptoms
		April 5	10% oxygen	No definite changes	Hyperventilation induced with 10% oxygen
			9% oxygen, 2% carbon dioxide	No definite changes	No symptoms
4	Coronary sclerosis	March 17	10% oxygen	T_1, T_2, T_4 lowered; S-T_1, S-T_2, S-T_4 depressed	Precordial pain
			10% oxygen, 3% carbon dioxide	S-T depression and lowering of T did not occur	No precordial pain

5	Coronary sclerosis	March 29	10% oxygen 9% oxygen, 3% carbon dioxide	T_4 diphasic; S-T_3 depressed No S-T_3 depression; T_4 more upright	
6	Coronary sclerosis and hypertensive vascular disease	April 12	10% oxygen 9% oxygen, 3% carbon dioxide	T_1, T_3 lowered T_1, T_2, T_4 higher	
7	Coronary sclerosis and hypertensive vascular disease	March 27	12% oxygen 10% oxygen, 2% carbon dioxide	No definite changes No definite changes	Precordial pain occurred in 15 minutes Breathed mixture 20 minutes without symptoms
8	Hypertensive vascular disease	March 14	10% oxygen 10% oxygen, 3% carbon dioxide	T_1, T_2 lowered; T_3 inverted T_1, T_2 higher; T_3 upright	
9	Coronary sclerosis and hypertensive vascular disease	April 22	12% oxygen 9% oxygen, 2% carbon dioxide	No definite changes No definite changes	
10	Coronary sclerosis?	April 17	10% oxygen 10% oxygen, 3% carbon dioxide	S-T_1 depressed; T_1, T_2, T_3 lowered; T_4 diphasic S-T_1 not depressed; T_1, T_2, T_3 higher; T_4 upright	Hyperventilation induced with 10% oxygen
		April 27	12% oxygen 9% oxygen, 3% carbon dioxide	T_1, T_4 slightly lower T_1, T_4 moderately lower	
11	Chronic nephritis	March 14	10% oxygen 10% oxygen, 3% carbon dioxide	T_1, T_2, T_4 inverted T_1, T_2 upright; T_4 diphasic	
		March 25	12% oxygen 10% oxygen, 2% carbon dioxide	No definite changes No definite changes	
		April 8	10% oxygen 9% oxygen, 2% carbon dioxide	T_1, T_2, T_3, T_4 lowered; T_4 diphasic T_3, T_4 diphasic	

TABLE I—CONT'D

CASE NO.	DIAGNOSIS	DATE OF OBSERVATION (1940)	GAS MIXTURE BREATHED	ELECTROCARDIOGRAPHIC CHANGES	REMARKS
12	Multiple sclerosis	March 18	10% oxygen	T_3 flat	
			10% oxygen, 3% carbon dioxide	T_3 upright	
13	Normal	March 12	10% oxygen	T_1, T_2, T_4 lowered	
			10% oxygen, 3% carbon dioxide	T_1, T_2, T_4 normal	
14	Normal	April 18	10% oxygen	T_2, T_4 lowered	
			10% oxygen, 3% carbon dioxide	T_2, T_4 normal	
15	Normal	April 19	10% oxygen	T_4 diphasic; T_1, T_2, T_3, T_4 lowered	10% oxygen and hyperventilation. Dizzy
			10% oxygen, 3% carbon dioxide	T_4 upright; T_1 T_2, T_3, T_4 higher	Comfortable
16	Normal	April 17	10% oxygen	T_1, T_2, T_4 lowered	Hyperventilation induced with 10% oxygen. Dizzy, faint
			10% oxygen, 3% carbon dioxide	Lowering of T_1, T_2, T_4 not present	No symptoms
17	Normal	April 17	10% oxygen	T_1, T_2, T_4 lowered	Dizzy
			10% oxygen, 3% carbon dioxide	T_1, T_2, T_4 lowered	Comfortable
18	Normal	April 19	10% oxygen	No definite changes	Hyperventilation induced
			10% oxygen, 3% carbon dioxide	No definite changes	
19	Normal	April 17	10% oxygen	No definite changes	Hyperventilation. Dizzy
			10% oxygen, 3% carbon dioxide	No definite changes	Comfortable
20	Normal	April 20	10% oxygen	T_2 inverted; S-T_2 depressed; T_1, T_4 lower	15-minute test
			10% oxygen, 3% carbon dioxide	T_2 upright; S-T_2 not depressed; T_4 higher	

did not occur when the low-oxygen mixture with carbon dioxide was inhaled, but appeared when the low-oxygen mixture alone was inhaled. Similarly, the depression of the T wave and S-T segment which was produced by straight anoxemia was not present when carbon dioxide was added to an even lower oxygen mixture (the electrocardiographic changes are illustrated by the second test in Case 1, Table I).

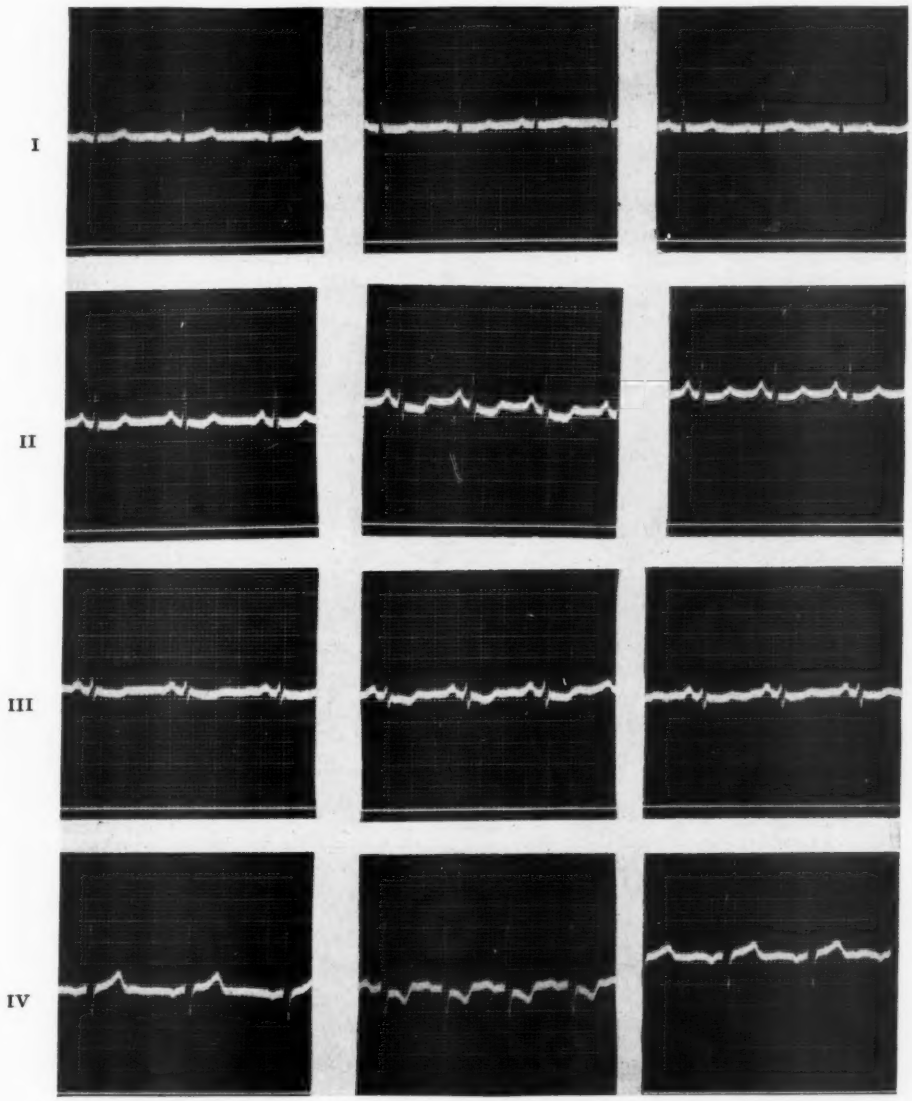

Fig. 1.—Electrocardiogram in Case 1. *A*, Control, T_1 upright, T_2 upright, T_3 diphasic, T_4 upright. *B*, After breathing a 10 per cent oxygen mixture for twenty minutes. T_1 upright but small, T_2 diphasic, S-T_2 depressed, T_3 diphasic, T_4 inverted, S-T_4 depressed. *C*, After breathing a mixture containing 10 per cent oxygen and 3 per cent carbon dioxide for twenty minutes. T_1 upright, T_2 upright, T_3 diphasic, T_4 upright; no S-T_2 or S-T_4 depression.

TABLE II

BLOOD GASES AND CLINICAL DATA AFTER INHALATION OF A 9 TO 12 PER CENT OXYGEN MIXTURE, WITH AND WITHOUT 2 TO 3 PER CENT CARBON DIOXIDE

CASE NO.	DATE (1940)	DIAGNOSIS	ARTERIAL OXYGEN			ARTERIAL CO_2 CONTENT (VOL. %)	pH	GAS MIXTURE USED	PULMONARY VENTILATION (C.C. PER MIN.)	BLOOD PRESSURE		PULSE		REMARKS
			CONTENT (VOL. %)	CAPACITY (VOL. %)	SATURATION (%)					START	END	START	END	
1	April 1	Coronary sclerosis	15.3	19.7	77.7	53.1	7.46	9.3% O_2-2% CO_2	12,000	140/100	156/100	80	90	No precordial distress
			13.5	19.7	68.5	50.6	7.52	10% O_2	12,520	140/ 90	143/ 95	78	88	Precordial distress
2	March 20	Coronary sclerosis and hypertensive vascular disease	15.6	15.3	100.0	44.9	7.45	Air	12,520	180/100		64		
			12.3	16.6	74.1	47.6	7.50	12% O_2	13,180	180/100	185/100	64	78	
			12.2	16.2	75.1	48.1	7.48	10% O_2-2% CO_2	20,300	180/ 95	195/100	72	80	
3	April 5	Coronary sclerosis	18.8	19.5	96.4	51.6	7.45	Air	5,410	120/ 80		86		
			14.7		73.2	49.8		9% O_2-2% CO_2	15,030	145/ 90	140/ 90	92	88	
			17.4	20.1	86.5	41.0	7.60	10% O_2	19,380	140/100	130/100	84	72	Hyperventilation induced
4	March 17	Coronary sclerosis						-0% O_2	8,900	130/ 56	144/ 94	76	86	Pain at 20 minutes
								10% O_2-3% CO_2	12,790	132/ 60	135/ 70	60	76	No pain
5	March 29	Coronary sclerosis	19.1	19.9	96.0	51.6	7.45	Air	8,770	210/110		72		
			13.1	20.0	65.5	50.2	7.53	10% O_2	12,780	205/110	230/120	76	80	Pain at 20 minutes
			16.5	20.5	80.5	52.0	7.46	9% O_2-3% CO_2	18,720	230/130	230/130	72	64	No pain
6	April 12	Coronary sclerosis and hypertensive vascular disease	20.3	21.0	96.7	47.4	7.47	Air	5,400			112		
			18.5	21.9	84.5	51.5	7.44	9% O_2-3% CO_2	14,700			102		
			17.7	21.9	80.8	45.3	7.54	10% O_2	12,260			112	120	

7	March 27	Hypertensive vascular disease	18.8	19.1	98.4	49.1	7.42	Air	7,970	160/100		72		
			15.3	19.5	78.5	48.1	7.43	12% O_2	12,530	160/100	160/100	72	92	Pain at 15 minutes
			16.0	19.9	80.4	48.0	7.47	10% O_2-2% CO_2	17,340	155/100	185/110	72	84	No pain
8	March 17	Syphilitic aortitis	15.5	15.7	98.7	54.7		Air						
			12.4	16.3	76.1	48.9		10% O_2	9,680	185/ 60	190/ 60			Pain at 5 minutes. Blood taken in 5 minutes
			13.9	16.3	85.3	51.9		10% O_2-3% CO_2	12,520					Pain at 5 minutes. Blood taken in 5 minutes
9	April 22	Coronary sclerosis and hypertensive vascular disease	13.6	13.8	98.5	44.1	7.47	Air	6,590					
								12% O_2	10,940	170/110	175/110	84	92	
			10.7	14.2	75.4	45.0	7.48	9% O_2-2½% CO_2	17,280				98	
10	March 19	Coronary sclerosis and hypertensive vascular disease	14.7	15.1	97.3	34.6	7.47	Air						
			9.9	16.1	61.5	31.7		10% O_2	20,900	240/ 80	220/ 65	40	44	
			12.4	15.9	78.0	32.4	7.44	10% O_2-2% CO_2	38,630		230/ 70			Blood taken in 15 minutes
11	March 25	Chronic nephritis	16.8	17.4	96.6	52.2	7.42	Air	7,180	135/100		80		
			12.8	17.1	74.9	52.4	7.47	12% O_2	8,830	135/100	130/ 90	80	100	
			11.7	16.7	70.1	49.7	7.44	10% O_2-2% CO_2	9,760	130/ 90	145/ 90	80	92	
	April 8		11.9	16.7	70.1	49.7	7.44	9% O_2-2% CO_2	13,180	125/ 85	130/ 80	108	116	
			11.5	17.3	67.5	49.3	7.55	10% O_2	13,450	125/ 90	132/ 66	88	108	Hyperventilation induced
12	April 23	Hypertensive vascular disease	18.0	18.4	97.9	51.0		Air		210/130		84		
			13.6	18.5	73.5	47.6		10.5% O_2		250/140	210/120	100	108	
			16.4	18.6	88.2	50.8		10% O_2-3% CO_2		203/120	240/130			
			15.7	19.2	81.8	45.7		13% O_2						
13	April 24	Coronary sclerosis?	16.6	17.2	96.5	51.2		Air		134/ 82		74		
			14.2	18.0	78.9	49.4		12% O_2			148/ 84		74	
			14.7	18.0	81.7	51.1		9% O_2-3% CO_2		146/ 84	144/ 86	76	74	

If the arterial oxygen saturation in both experiments were precisely the same, the conclusion might be reached that the relative alkalosis which was present after inhaling the 10 per cent oxygen mixture was the significant factor in the production of both precordial pain and electrocardiographic changes. In that event, an assumption might be made that alkalosis had caused either contraction of the coronary arteries or constriction of the capillary bed, with progressive tissue ischemia and aggravated anoxia, and that these pathologic events were prevented by the inhalation of small amounts of carbon dioxide. Although an arterial oxygen saturation of 77.7 per cent represents severe anoxemia, which, in other cases of coronary disease, is sufficient to produce both precordial pain and electrocardiographic changes, the fact that this arterial oxygen saturation was higher than that which obtained when carbon dioxide was added makes possible the assumption that a more severe anoxemia might have been necessary to produce precordial pain and electrocardiographic changes in this particular case.

In Case 2, the arterial oxygen saturation was comparable in the two experiments, namely, 74.1 per cent after inhalation of a 12 per cent oxygen mixture, and 75.1 per cent after inhalation of a 10 per cent oxygen and 2 per cent carbon dioxide mixture. The pH was also higher after inhalation of a low oxygen mixture than it was after a low oxygen and carbon dioxide mixture, i.e., 7.50 as compared to 7.48. The presence of 2 per cent carbon dioxide did not completely prevent an alkaline shift, for the control pH was 7.45. Nevertheless, the electrocardiographic changes were much less after inhalation of the low-oxygen carbon dioxide mixture than after low oxygen alone (the electrocardiographic changes are shown in the second test in Case 2, Table I).

The interpretation of the results in this case appears to be that arterial anoxemia and alkalosis produced more marked electrocardiographic changes than anoxemia alone, and this suggests again that the alkaline shift caused by acute anoxia results in constriction of the capillary bed, additional ischemia, and progressive anoxia of the cardiac muscle. One other physiologic event must be borne in mind, namely, that alkalosis itself increases tissue anoxia, because oxygen is held more firmly to hemoglobin when the blood is more alkaline; thus, when a low-oxygen mixture is inhaled with carbon dioxide, more oxygen is liberated to the tissues even when the arterial oxygen saturation is identical in both cases. It must be admitted, therefore, that the oxygen tension of the cardiac muscle was higher when the low-oxygen carbon dioxide mixture was inhaled than when an even higher oxygen percentage was breathed without carbon dioxide. Conceivably, therefore, the more marked changes in the electrocardiogram caused by breathing the 12 per cent oxygen mixture, as compared to 10 per cent oxygen and 2 per cent carbon dioxide, may be explained by more severe tissue anoxia, without necessarily hypothesizing constriction of the capillary bed. However,

since alkalosis has been shown to produce constriction of capillaries in other parts of the body, it seems reasonable to assume that the same physiologic action may have exerted itself in the coronary circulation.

In Case 3, hyperventilation was induced while the patient was breathing a 10 per cent oxygen mixture; the pulmonary ventilation was 19,380 c.c. per minute, as compared to 15,030 when a 9 per cent oxygen and 2 per cent carbon dioxide mixture was breathed. No change was produced in the electrocardiogram by overventilation plus anoxemia, although the arterial carbon dioxide content fell from 51.6 to 41.0 volumes per cent and the pH increased from 7.45 to 7.60. The arterial oxygen saturation was relatively high, i.e., 86.5 per cent. The result in this case would suggest that alkalosis without severe anoxemia may be insufficient to produce precordial pain or electrocardiographic changes.

In Case 5, both precordial pain and electrocardiographic changes were produced by the inhalation of a 10 per cent oxygen mixture; these did not occur after inhalation of a 9 per cent oxygen and 3 per cent carbon dioxide mixture. The relative alkalosis produced by inhaling a 10 per cent oxygen mixture was prevented when carbon dioxide was added to an even lower oxygen mixture. However, increased pulmonary ventilation with the carbon dioxide mixture was associated with an arterial oxygen saturation of 80.5 per cent, as compared to 65.5 per cent when the 10 per cent oxygen mixture was breathed. As in Case 1, the higher oxygen tension of the arterial blood, rather than the more acid pH, may have accounted for the absence of symptoms.

In Case 6, the results were similar to those in Case 2, namely, with approximately comparable arterial oxygen saturations the electrocardiographic changes were more marked when a 10 per cent oxygen mixture was breathed, and the pH was 7.54, than when a 9 per cent oxygen and 3 per cent carbon dioxide mixture was inhaled, and the pH was 7.44.

In Case 7, with nearly comparable arterial oxygen saturations, precordial pain was experienced after the inhalation of a 12 per cent oxygen mixture, and not after 9 per cent oxygen with 2.5 per cent carbon dioxide.

In Case 8, a patient with syphilitic aortitis, pain was induced at the end of five minutes, both after the inhalation of a 10 per cent oxygen mixture and 10 per cent oxygen with 3 per cent carbon dioxide. In the latter experiment, the arterial oxygen saturation was 85.3 per cent, with an arterial carbon dioxide content of 51.9 volumes per cent; in the former (10 per cent oxygen), the arterial oxygen saturation was 76.1 per cent, with a carbon dioxide content of 48.9 volumes per cent. In other words, with constriction presumably present at the mouths of the coronary arteries, pain came on quickly irrespective of the blood gas changes. In a previous report[3] it was noted that pain came on quickly in two cases of aortic stenosis, and in these cases the circulation time was not short-

ened. In most other cases of heart disease the circulation time was appreciably faster after the inhalation of a 12 per cent oxygen mixture.

In Cases 9 to 13 the blood gas changes could not be significantly correlated with clinical or electrocardiographic observations except in the last test in Case 11, in which there were less marked electrocardiographic alterations with a low-oxygen carbon dioxide mixture than with low oxygen alone; the arterial oxygen saturations were approximately comparable, and there was an alkaline shift of the pH during the inhalation of the low-oxygen mixture.

The blood pressure and the pulse rate showed no significant changes as a result of inhaling low-oxygen mixtures, either with or without carbon dioxide. In some cases the pulse rate was elevated. The pulmonary ventilation was markedly increased as a result of addition of small percentages of carbon dioxide in all cases except Case 1.

Before discussing the physiologic significance of the above results, the effect on the electrocardiogram of inhaling (1) pure oxygen, and (2) a mixture of 97 to 96 per cent oxygen and 3 to 4 per cent carbon dioxide should be presented (Table III). Observations were made on thirty-two patients who had primary heart disease, or whose cardiac function was affected by pulmonary or other disease. There were six normal and two miscellaneous subjects.

Of the thirty-two subjects in the cardiac group, twenty-five responded to the inhalation of either pure oxygen, or a mixture of 97 to 96 per cent oxygen and 3 to 4 per cent carbon dioxide, with either elevation of the T wave in one or more of the four leads, less inversion of the T wave, or a change from a diphasic to an upright T wave. In five cases there was no change after inhalation of either oxygen or oxygen with carbon dioxide. In one case, T_1 was very slightly lower after both tests, and, in another instance, T_3 was very slightly lower after oxygen and very slightly higher after oxygen with carbon dioxide.

In Table III an elevation of the T wave of 0.5 mm. ±0.25 mm. is noted as +; an elevation of 1.0 mm. ±0.25 mm. is noted as ++; an elevation of 1.5 mm. ±0.25 mm. is noted as +++; and an elevation of 2 mm. is noted as ++++.

Of twenty cases in which the electrocardiographic changes caused by pure oxygen were compared with those which resulted from oxygen plus carbon dioxide, there were seven in which the T-wave elevation was higher with pure oxygen, one in which it was very slightly higher with the oxygen plus carbon dioxide mixture, and twelve in which the result was approximately the same. In the twelve instances in which the elevation of the T wave was noted as being equal after the two tests, the impression was frequently gained that there was very slight lowering of the T wave when carbon dioxide was added to the oxygen mixture. It was believed, however, that changes of a magnitude of 0.25 mm. were too small to be considered significant.

TABLE III

EFFECT OF INHALATION OF PURE OXYGEN AND OF A HIGH OXYGEN LOW CARBON DIOXIDE MIXTURE ON THE FORM OF THE ELECTROCARDIOGRAM

CASE NO.	DIAGNOSIS	ELECTROCARDIOGRAPHIC CHANGES AFTER 20 MINUTES' INHALATION OF	
		PURE OXYGEN	96% OXYGEN WITH 4% CO_2
1	Coronary sclerosis Second test	T_4 higher, + T_4 higher, +++	T_4 higher, +*
2	Pulmonary emphysema Second test	T_3 higher, ++ T_3 higher, ++	T_3 higher, + T_3 higher, +
3	Arteriosclerotic heart disease	T_4 higher, +; T_1, T_2, previously diphasic, upright	T_4 higher, +; T_1, T_2, previously diphasic, upright
4	Arteriosclerotic heart disease	No change	No change
5	Hypertensive vascular disease and cardiac insufficiency	T_1, T_2 less diphasic; T_4 previously inverted, upright	T_1, T_2 less diphasic; T_4, previously inverted, upright
6	Pulmonary fibrosis	T_2, previously diphasic, upright	T_2, previously diphasic, upright
7	Coronary sclerosis		T_3 less inverted; T_4 higher*
8	Coarctation of aorta	T_4 higher, ++	T_4 higher, +
9	Coronary sclerosis?	T_4 higher, +	T_4 higher, +
10	Hyperthyroidism	T_4, previously diphasic, higher, +	T_4, previously diphasic, higher, +
11	Coronary occlusion	T_4 higher, ++	T_4 higher, +
12	Coronary sclerosis	T_1, T_4 less inverted	T_1, T_4 less inverted
13	Arteriosclerotic heart disease	T_4 higher, ++; T_3 lower, -	T_4 higher, +; T_3 lower, -; T_1 less inverted
14	Hypertensive vascular disease	No change	No change
15	Coronary sclerosis	T_1 less inverted; T_2 higher, ++	T_2 higher, +
16	Coronary occlusion	No change	T_3 higher, +
17	Splenic vein thrombophlebitis	T_3 higher, ++; T_4 higher, +++	T_3 higher, +; T_4 higher, ++
18	Beck's sarcoid	T_1, T_2 higher, ++; T_4 less inverted	T_1, T_2 higher, +; T_4 less inverted
19	Coronary sclerosis		T_3 previously diphasic, upright; T_2, T_4 higher, ++†
	Second test	No change	No change
20	Coronary sclerosis	T_3 slightly lower, -	T_3 higher, +*
21	Coronary thrombosis	T_1 lower, -	T_1 lower, -
22	Coronary sclerosis	T_4 higher, ++	T_4 higher, +
23	Arteriosclerotic heart disease	T_3 less inverted	Questionable change*
24	Hypertensive vascular disease	T_4 higher, ++ T_1, T_2 less inverted	T_4 higher, +; T_1, T_2 less inverted
25	Coronary sclerosis	T_1, T_2 higher, +; T_4 higher, ++	T_1, T_2 higher, +; T_3 higher, +
26	Tuberculous pericarditis	T_2, T_4 higher, +	T_2 higher, +

TABLE III—CONT'D

CASE NO.	DIAGNOSIS	ELECTROCARDIOGRAPHIC CHANGES AFTER 20 MINUTES' INHALATION OF	
		PURE OXYGEN	96% OXYGEN WITH 4% CO_2
27	Intermittent claudication	No change	No change
28	Asthma	No change	No change*
29	Coronary sclerosis	T_1 higher, + T_2 higher, ++ T_3 higher, + T_4 higher, +	
	Second test‡	T_1 higher, + T_2 higher, ++++ T_4 higher, +	
30	Hypertensive cardial vascular disease	T_1 higher, +	
	Second test‡	T_1 higher, ++ T_2 higher, ++	
31	Coronary sclerosis	T_1 higher, ++ T_2 higher, ++ T_4 higher, +	
32	Acute infarction of anterior surface of the heart	No change	
	Second test‡	T_2 higher, +	
33	Coronary sclerosis	T_4 higher, ++	
	Second test‡	T_1 higher, + T_4 higher, +++	
34	Hypertensive cardial vascular disease	T_4 higher, ++	
	Second test‡	T_4 higher, ++++	
35	Normal	No change	No change
36	Normal	No change	No change
37	Normal	No change	T_2 lower, -
38	Normal	No change	No change
39	Normal	T_1, T_2 higher, ++; T_3, T_4, higher, ++++	T_1, T_2, T_3, T_4 higher, +
	Second test	T_2, T_3 higher, ++; T_4 higher, ++++	T_2, T_3, T_4 higher, +*
40	Normal	T_2 higher, ++	T_1, T_4 lower, -

*97 per cent oxygen with 3 per cent carbon dioxide was used.
†Patient under intermittent oxygen treatment.
‡After 30 minutes of pure oxygen.

In the group of two cases of miscellaneous disease and six normal persons there was no change as the result of inhaling pure oxygen in six cases, and elevation of the T wave in two cases. In four of five cases in the group no change resulted from inhalation of the oxygen carbon dioxide mixture in 4; elevation of the T wave occurred in one, and lowering in two. The changes were less frequent in the control group, but in one instance there was definite elevation of the T wave in all four leads, and slightly less marked T-wave elevation after inhalation of the oxygen carbon dioxide mixture. An illustration of the effect of pure oxygen on the electrocardiogram is shown in Fig. 2. It will be observed that the T waves in Leads I, II, and IV are of greater amplitude than in the control tracing.

COMMENT

The induction of acute anoxia in patients with heart disease has been shown to produce overbreathing, a decrease in arterial carbon dioxide, and a shift in pH toward the alkaline side. To counteract the loss of

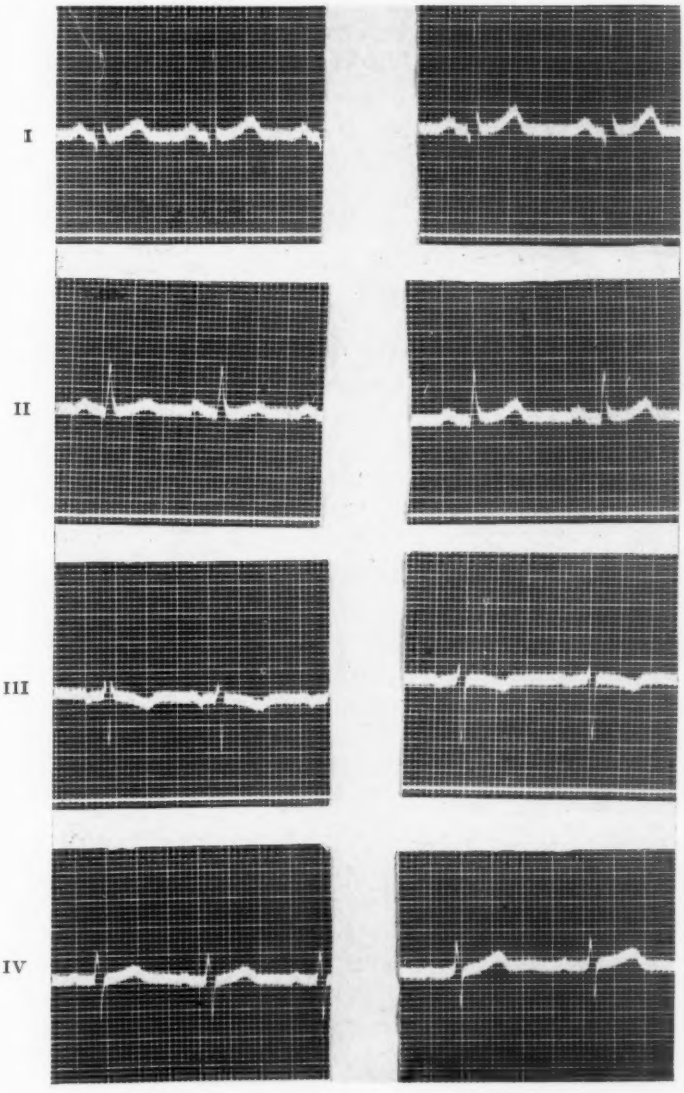

Fig. 2.—Electrocardiogram in Case 31. *A*, Control. *B*, After breathing pure oxygen for fifteen minutes. T_1, T_2 are 1 mm. higher than the control, and T_4 is 0.5 mm. higher.

carbon dioxide, low-oxygen mixtures were inhaled with the addition of 2 to 3 per cent carbon dioxide. This procedure compensated for the undue elimination of carbon dioxide which overbreathing otherwise

produced, and prevented or decreased the alkaline shift of the blood pH. The stimulating effect of carbon dioxide on the volume of ventilation increased the arterial oxygen saturation above that which was found when a similar oxygen concentration was inhaled with carbon dioxide. In order to ascertain whether alkalosis played a role in the causation of the clinical and electrocardiographic changes of induced oxygen want, an attempt was made to produce a similar degree of arterial anoxemia in patients who had an alkaline shift in pH and in patients in whom such a shift had been prevented by carbon dioxide in the low-oxygen mixture. This was done by lowering the oxygen percentage of the mixture in which carbon dioxide was employed.

When symptoms or electrocardiographic changes resulted from inhalation of a 10 to 12 per cent oxygen mixture, repetition of the test with the addition of 2 to 3 per cent carbon dioxide prevented these changes in the majority of patients with coronary disease. In most of the cases (eight out of twelve), the arterial oxygen saturation was somewhat higher when carbon dioxide was employed. In four cases, however, in which the degree of arterial anoxemia was made comparable by administering less oxygen with the carbon dioxide than with the plain low-oxygen mixture, either no symptoms occurred or the electrocardiographic changes were less marked, in the patients who received carbon dioxide, and, therefore, in the cases in which an undue loss of carbon dioxide and alkaline shift in pH were prevented.

These results suggest that the alkalosis of induced anoxemia may be a factor in impairing the coronary circulation, either by causing constriction of the capillary bed or possibly by increasing the tendency toward coronary spasm. Since vasoconstriction of capillaries has been reported as the result of loss of carbon dioxide from the circulating blood, induced oxygen want in patients with coronary disease may be followed by a vicious train of pathologicophysiologic events: arterial anoxemia, hyperventilation, loss of dissolved carbon dioxide, alkaline shift of blood pH, capillary (or possibly coronary) blood vessel constriction, ischemia, and progressive tissue anoxia. It is altogether likely that tissue oxygen want is the ultimate significant factor in the causation of the symptoms and signs of coronary insufficiency. Although tetany can be produced by hyperventilation in normal subjects, it will not occur if the hyperventilation is conducted during the breathing of pure oxygen. In other words, alkalosis in the presence of a high oxygen tension is not productive of tetany.

In a study by Kerr, et al.,[21] hyperventilation was used to produce anxiety states and psychoneurotic symptoms. Among their cases was a patient with coronary disease who developed precordial pain after hyperventilation. In three of our cases of coronary sclerosis, hyperventilation for twenty minutes failed to produce precordial pain or electrocardiographic changes. In one case, hyperventilation was induced

with a 10 per cent oxygen mixture, and, although the pH shifted from 7.45 to 7.60, no precordial pain or electrocardiographic changes took place; the arterial oxygen saturation in this case was elevated as a result of increasing the volume of ventilation to 86.5 per cent.

These results suggest that hyperventilation is more likely to be harmful when it is combined with severe anoxemia. In the case of syphilitic aortitis, pain occurred promptly after five minutes of inhaling the low-oxygen mixture, whether or not it contained 3 per cent carbon dioxide. In this instance, constriction of the capillary bed or contraction of the wall of the coronary arteries was evidently not involved, for carbon dioxide exerted no effect; narrowing of the mouths of the coronary arteries presumably produced a type of constriction that could not be compensated for by increased diameter of the coronary or smaller peripheral blood vessels. In other words, the ischemia was not appreciably influenced by the addition of carbon dioxide, even though the arterial anoxemia was diminished (85.3 per cent, as compared to 76.1 per cent when the 10 per cent oxygen mixture was inhaled without carbon dioxide). The fact that the increased oxygen tension in the blood when carbon dioxide was added did not delay the time of appearance of precordial pain indicates the importance of ischemia as a factor in coronary insufficiency (i.e., in the case of constriction at the mouths of the coronary arteries); conversely, the prevention of the symptoms of coronary insufficiency by adding 2 to 3 per cent carbon dioxide to the low-oxygen mixture in cases of coronary sclerosis suggests that loss of dissolved carbon dioxide is of importance in the regulation of the circulation through the coronary arteries and the tissue capillaries.

Since the inhalation of carbon dioxide had the beneficial effects which have been discussed, the effect of a mixture of 2 to 3 per cent carbon dioxide and 98 to 97 per cent oxygen was tried clinically, with respect to its effect on the electrocardiogram.[11] There are insufficient data to draw a conclusion at this time; however, it was observed that the T wave was elevated by inhaling the above mixtures, although generally not to the extent produced by the inhalation of pure oxygen. An explanation of these results was suggested by Macleod in a conversation concerning the physiologic significance of the changes we had found. The studies of Wilson, Macleod, and Barker[22] and later studies of Macleod[23] led to the opinion that a prolongation of the recovery period of cardiac muscle, with a delay in the oxidation of the products of metabolism, was one of the factors responsible for lowering of the T wave. According to this thesis, the inhalation of low-oxygen mixtures might delay the oxidation of products of metabolism. The addition of CO_2 to the low-oxygen mixtures would result in a lessening of tissue anoxia by preventing alkalosis, constriction of the capillary bed, and ischemia. In addition, the more acid pH of the blood, carrying an increased carbon dioxide tension, would unload oxygen into the tissues at a lower oxygen satura-

tion than blood in a more alkaline state. The T wave, therefore, was more upright, since tissue anoxia was relieved in some degree. Macleod's explanation may also apply to the occurrence of an elevation of the T wave during inhalation of sure oxygen in certain cases of coronary sclerosis; the increased oxygen tension may shorten the recovery period of cardiac muscle that might previously have been exposed to ischemic conditions. Admittedly, many other influences modify the height of the T wave, such as heat and cold,[24] and it is not the intention of this paper to offer a complete explanation of the mechanism of the T-wave deflection. That the tension of oxygen in the blood entering cardiac muscle was a determining factor in the direction and height of the T wave was an occurrence for which we sought an explanation; the clue given us by Macleod seemed consistent not only with our results, but with what is generally known in respect to the function of oxygen in muscle physiology.

SUMMARY

By means of blood gas and electrocardiographic observations, the physiologic action of oxygen and carbon dioxide on the coronary circulation was studied. When a deficiency of oxygen has been produced in the arterial blood by decreasing the oxygen concentration of inspired air, certain compensating mechanisms become manifest, such as an increase in pulmonary ventilation and circulation velocity. In cases of coronary sclerosis, the narrowed lumina of the coronary arteries impose a variable degree of obstruction to an increase in the flow of blood. The induction of oxygen want in the presence of this relative ischemia results in severe anoxia of the heart muscle, the consequences of which are (1) coronary insufficiency, with precordial pain and cardiac or peripheral circulatory failure, and (2) electrocardiographic changes, particularly lowering of the T wave or depression of the S-T segment.

The increased pulmonary ventilation produced by acute anoxia engenders a disproportionate loss of dissolved carbon dioxide, with a shift in blood pH toward the alkaline side. Since alkalosis produced by hyperventilation has been shown to cause constriction of capillaries in other parts of the body, the possibility that it may have the same effect on the coronary circulation was investigated. The addition of small amounts of carbon dioxide, such as 2 to 3 per cent, to a low-oxygen mixture prevented the clinical and electrocardiographic signs of coronary insufficiency which have been described above. Although the inhalation of a low-oxygen carbon dioxide mixture in eight out of ten cases of coronary disease resulted in a higher arterial oxygen saturation than the inhalation of a comparable low-oxygen mixture, there were four cases in which the symptoms or electrocardiographic signs of coronary insufficiency either did not occur, or were diminished, in the presence of a comparable, severe arterial anoxemia, when carbon dioxide loss was prevented.

The inhalation of high-oxygen concentrations is known to improve the function of the coronary circulation when it has been previously impaired. The electrocardiographic effects of the inhalation of approximately pure oxygen in thirty-two cases of coronary disease were studied. In twenty-seven cases, the T wave was rendered more upright. The addition of carbon dioxide to high-oxygen concentrations either had no effect, or, in six cases, diminished slightly the T-wave elevation produced by inhaling high-oxygen mixtures.

Accepting Macleod's thesis that one of the factors influencing the height of the T wave is the speed of recovery of cardiac muscle, we tentatively conclude that the evidence obtained in these studies suggests that the inhalation of low-oxygen mixtures prolongs the recovery period of heart muscle in patients with coronary disease, and that the inhalation of high-oxygen mixtures shortens the recovery period. In the presence of acute anoxia, the inhalation of small amounts of carbon dioxide shortens the recovery period of cardiac muscle, in part by increasing the arterial oxygen tension, and in part by preventing constriction of capillaries in the coronary circulation. The administration of carbon dioxide in the absence of alkalosis may in some cases delay the recovery period of heart muscle.

NOTE: Since the submission of this paper to the AMERICAN HEART JOURNAL, ten additional normal subjects have been tested after inhaling pure oxygen for twenty minutes. In six cases there was an increase in the height of the T wave in two or more leads; in four, there was no change. Of ten additional cases of heart disease, there was an increase in the height of the T wave in one or more leads in six, and in four cases no change was observed.

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THE DURATION OF ELECTRICAL SYSTOLE (Q-T INTERVAL) IN CASES OF MASSIVE PERICARDIAL EFFUSION

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IN CLINICAL practice the differentiation between pericardial effusion and cardiac dilatation is often difficult, and may be impossible.[1-3] Pericardial effusion has often been mistaken for cardiac enlargement even after a careful roentgenologic examination, and vice versa. In fact, pericardial paracentesis has not infrequently been attempted in cases of cardiac dilatation; in one such case in this hospital, necropsy revealed no pericardial disease, but, instead, a large tear of the right ventricular wall which had been caused by the exploratory needle. Moreover, pericardial paracentesis has frequently not been done on patients with large pericardial effusions when this procedure was definitely indicated from both diagnostic and therapeutic viewpoints. Such mistakes appear unavoidable in some instances, for the physical and radiologic signs may be alike in the two conditions. In both cases there are often similar cardiac contours, feeble cardiac activity, a small pulse pressure, and congestive heart failure.[4] Any objective criterion which may aid in differentiating cardiac dilatation with congestive failure from massive pericardial effusion with similar congestive phenomena will have certain theoretical and practical importance.

It occurred to me that, as there is a fundamental difference between the cardiodynamics of congestive heart failure associated with cardiac dilatation and those of pericardial effusion and compression of the heart (cardiac tamponade), such a difference might be reflected in the duration of electrical systole, as measured by the Q-T interval of the electrocardiogram, taking the cardiac rate into consideration. The ordinary type of congestive heart failure is characterized by an outflow stasis. In this condition, although the heart is dilated, and there is an increase in both its systolic and diastolic volume, systole is insufficient and the cardiac output is subnormal.[5, 6] In the electrocardiogram a relative prolongation of electrical systole at the expense of diastole has been demonstrated.[7] In congestive failure caused by a large pericardial effusion and compression, the reverse, i.e., an inflow stasis, exists. The heart is compressed by the fluid under tension, so that diastolic relaxation is incomplete. This produces a decrease of both the systolic and diastolic volume of the heart, and results also in a subnormal cardiac output and venous congestion behind the heart.[4, 8] Ventricular systole is normal as far as ejection is concerned, but is insufficient because the diastolic filling is inadequate. The relative duration of electrical systole in such

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cases has not hitherto been studied, as far as I am aware, but, on theoretical grounds alone, one would expect it to be different from that in cases of myocardial failure. With this in mind the following study was made.

MATERIAL AND METHODS

In order to make this series of cases a simple and homogeneous one, only cases of massive tuberculous pericardial effusion, with signs of cardiac tamponade, such as peripheral venous congestion, hepatomegaly, dependent edema, and, in some cases, ascites, were included. Venous congestion was considered to be moderate when there were engorged cervical veins, an enlarged and tender liver, and slight edema of the legs; it was regarded as pronounced when, in addition, ascites and moderate or marked edema of the legs were present. In most cases there was dyspnea of varying severity. Cases of rheumatic pericarditis and purulent pericarditis were excluded from this study because, in the former, the pericardial effusion is usually too small to have a hydrostatic effect on the heart, and, in the latter, the amount of pus may be small or large, and there is a more extensive complicating subpericardial myocarditis than occurs with tuberculous effusion. Cases of constrictive pericarditis were also excluded because there were only two available for study in which the diagnosis was confirmed at autopsy; furthermore, in this condition the cardiac systole may not be entirely normal.[9] All patients were observed in the hospital and had careful roentgenologic examinations. Only cases in which the presence of a large pericardial effusion was proved by pericardial paracentesis, or at necropsy, or both, were included in this study. In five cases the diagnosis of a large, tuberculous, pericardial effusion was confirmed at necropsy. In five, tubercle bacilli were recovered from guinea pigs which had been inoculated with pericardial fluid obtained by paracentesis. Pericardial paracentesis was performed on each patient; the number of paracenteses varied from one to sixteen per patient. In all cases large amounts of pericardial fluid (serosanguineous in all but one, which was cloudy) were removed; the amount usually removed was 400 to 800 c.c. In several cases air was injected after the aspiration of fluid, and was found to be in the pericardial cavity on subsequent roentgenologic examinations. The roentgenograms of two patients in this series are reproduced to illustrate the contour of the pericardial sac which was generally observed in the cases reported (Figs. 1-3).

The electrocardiograms were usually taken soon after admission, before any therapeutic measures were carried out. Cases in which digitalis was administered before the record was taken were excluded from this study. Only those electrocardiograms which were taken at a time when the patients were afebrile or had only a subfebrile temperature were included, although the duration of electrical systole was similar in a given case whether or not fever was present. As the amount of fluid withdrawn was usually not maximal, and as electrocardiograms were usually not taken soon after paracentesis, no study was made of any possible change in electrical systole after removal of the fluid. The usual three leads were taken with the patient recumbent or semirecumbent, using the string galvanometer (Hindle). The resistance was always satisfactorily low. The string was standardized so that a current of one millivolt gave a deflection of one centimeter on the film. The study of the electrocardiograms was particularly centered on the amplitude and duration of the QRS and T waves, the Q-T level, the R-R interval and the Q-T interval. The voltage of QRS was considered low when it was less than 5 mm. in the lead showing the greatest amplitude.[10] T waves were regarded as low when they were less than 1 mm. in height. Measurements of the R-R and Q-T intervals of the same four consecutive cycles were made under a magnifying glass, in most cases, in Lead II, and, in some cases, in Lead I or III if T waves were not sharp enough in

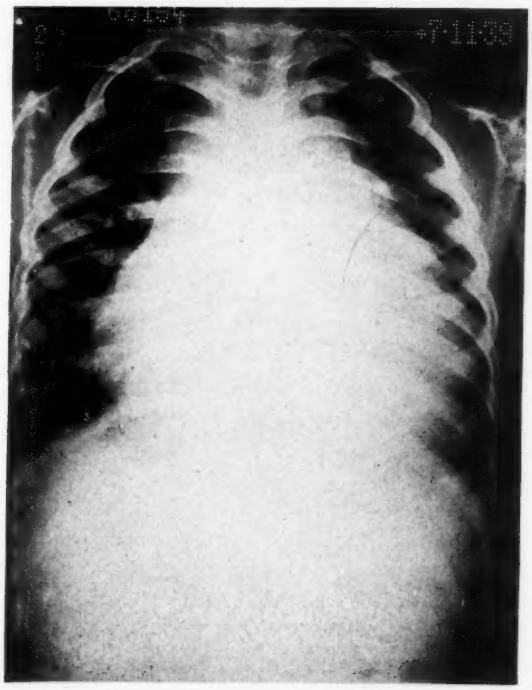

Fig. 1.—Case 7, July 11, 1939. Roentgenograph of the chest, showing massive tuberculous pericardial effusion before paracentesis.

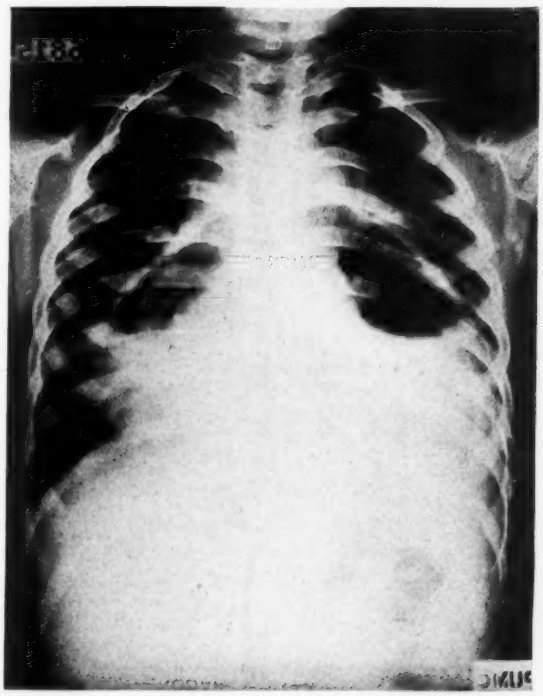

Fig. 2.—Case 7, July 17, 1939. After two pericardial paracenteses. On July 13, 500 c.c. serosanguineous fluid removed. On July 17, 600 c.c. of similar fluid removed and 250 c.c. of air injected. Tubercle bacilli recovered on guinea pig inoculation.

Lead II. The average of the four was taken. Some of the measurements of the Q-T interval were difficult and perhaps inaccurate, although they were probably not far from the figures given in Table I. The "predicted Q-T interval" (Adams) was calculated according to the straight line formulas of Adams for normal males and females.[11] The formula for males was:

$$Q—T = 0.1536\ R—R + 0.2462 \pm 0.012\ S.E.$$

That for females was:

$$Q—T = 0.1259\ R—R + 0.2789 \pm 0.014\ S.E.$$

The constant "K" was calculated according to the formula:

$K = Q—T \div \sqrt{R—R}$.[12] The electrocardiograms of some of the patients in this series are reproduced in Figs. 4 to 11.

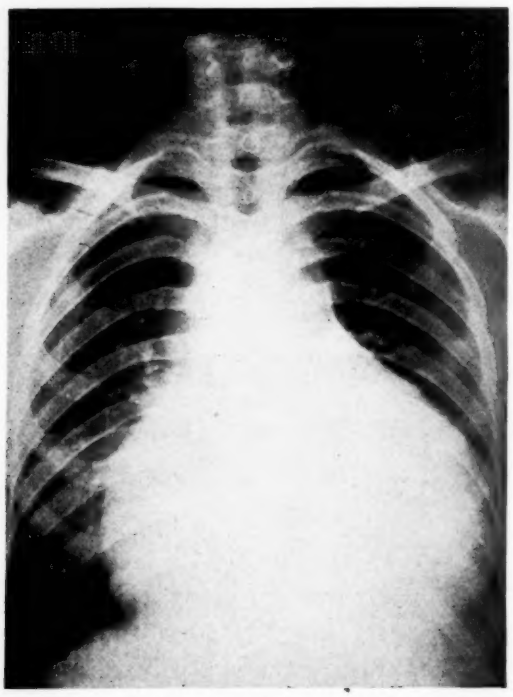

Fig. 3.—Case 10, October 12, 1933. Roentgenograph of the chest, showing massive tuberculous pericardial effusion before paracentesis. Necropsy later confirmed the diagnosis.

RESULTS

The important clinical and electrocardiographic observations are summarized in Table I. It will be seen that, as the systolic arterial pressure tended to be low and as the diastolic remained at about the normal level for Chinese, the pulse pressure was small (mean systolic, 93 mm., mean diastolic, 68 mm., and mean pulse pressure, 25 mm. Hg). The pattern of the electrocardiograms in this series corresponded to what has been noted by others.[13-20] The typical electrocardiogram showed low voltage of QRS, and a low, flat, or inverted T in the standard leads. Low voltage of QRS was not such a constant occurrence as alteration of T deflections,

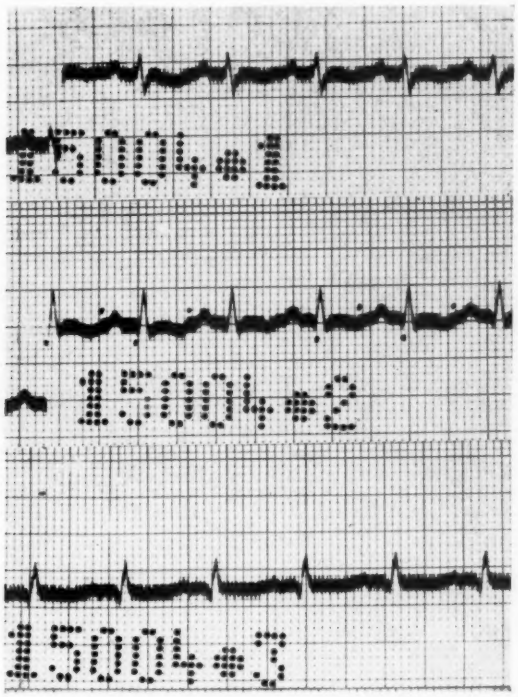

Fig. 4.—Electrocardiogram in Case 1. The Q-T interval is marked with two dots.

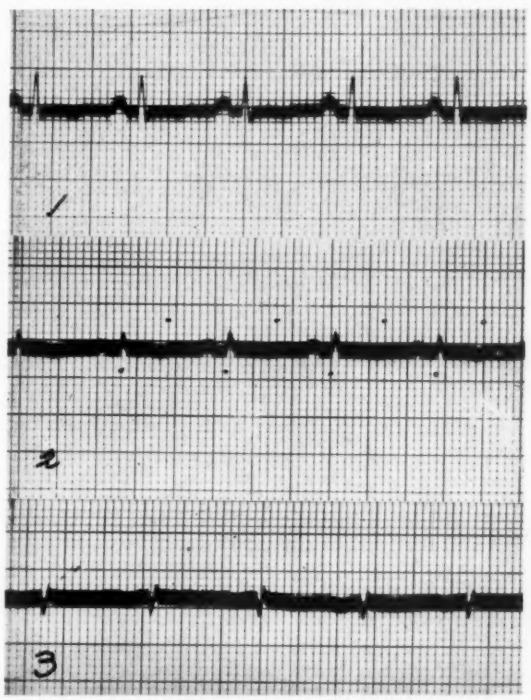

Fig. 5.—Electrocardiogram in Case 2.

TABLE I

CLINICAL AND ELECTROCARDIOGRAPHIC DATA ON FOURTEEN PATIENTS WITH TUBERCULOUS PERICARDIAL EFFUSION

NO.	SEX	AGE (YEARS)	VENOUS CONGESTION	ARTERIAL PRESSURE (MM. HG.)	NO. OF PERICARD. PARA-CENTESES	P-R INTERVAL (SEC.)	R-R INTERVAL (SEC.)	Q-T INTERVAL (SEC.)	PREDICTED Q-T INTERVAL (ADAMS) (SEC.)	DIF-FERENCE (PER CENT)	CON-STANT K*	REMARKS
1	M	32	Marked	90/55	16	0.15	0.460	0.264	0.317	-17	0.389	Low voltage QRS Inverted T all leads
2	M	10	Marked	94/64	3	0.13	0.544	0.254	0.330	-23	0.344	Low voltage QRS Short Q_3; inverted T_1, T_2; flat T_3
3	M	10	Moderate	90/72	1	0.12	0.550	0.322	0.331	- 3	0.434	Normal voltage QRS Low R_1; flat T_3
4	M	38	Moderate	96/80	1(N)	0.13	0.475	0.260	0.319	-18	0.375	Low voltage QRS Low T_2; flat T_3
5	M	16	Marked	100/78	1	0.16	0.560	0.280(?)	0.322	-16(?)	0.374(?)	Low voltage QRS Low T all leads
6	F	12	Moderate	94/66	2	0.16	0.480	0.258	0.339	-24	0.372	Low voltage QRS Inverted T_1, T_2 Flat T_3

7	M	8	Moderate	104/68	3(TB)	0.13	0.514	0.306	0.325	- 6	0.427	Low voltage QRS R.A.D. (slight) Low T_1; flat T_2 Inverted T_3
8	M	25	Marked	92/78	5(TB)	0.15	0.510	0.290	0.324	-10	0.406	Low voltage QRS Low T all leads
9	M	52	Moderate	80/62	4(N)(TB)	0.16	0.530	0.294	0.328	-10	0.404	Low voltage QRS Low to flat T waves
10	F	14	Marked	74/48	5(N)(TB)	0.16	0.500	0.284	0.342	-17	0.402	Low voltage QRS Inverted T all leads
11	M	24	Marked	90/80	1(N)	0.15	0.556	0.306	0.332	- 8	0.410	Low voltage QRS Inverted T all leads
12	M	24	Moderate	110/70	1	0.16	0.736	0.310	0.359	-14	0.361	Normal voltage QRS Low T all leads Deep Q_3
13	M	23	Marked	94/74	3(TB)	0.18	0.478	0.276	0.320	-14	0.399	Normal voltage QRS Inverted T_1, T_2
14	F	25	Marked	90/55	3(N)	0.18	0.450	0.272	0.336	-19	0.405	Low R_1. Low T_1 Inverted T_2, T_3

*$K = Q—T \text{ interval} \div \sqrt{\overline{R\text{-}R} \text{ interval}}$.

N, Necropsy; TB, tubercle bacilli recovered on guinea pig inoculation.

Roentgenologic examination showed abnormalities which were typical of massive pericardial effusion in all except Case 4.

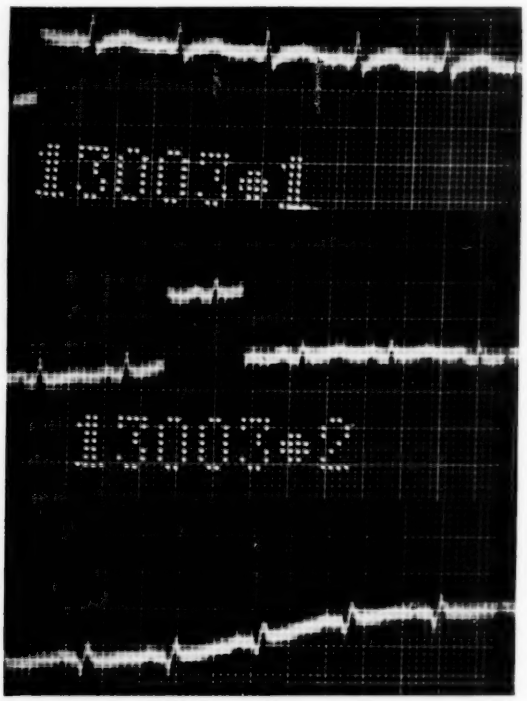

Fig. 6.—Electrocardiogram in Case 4.

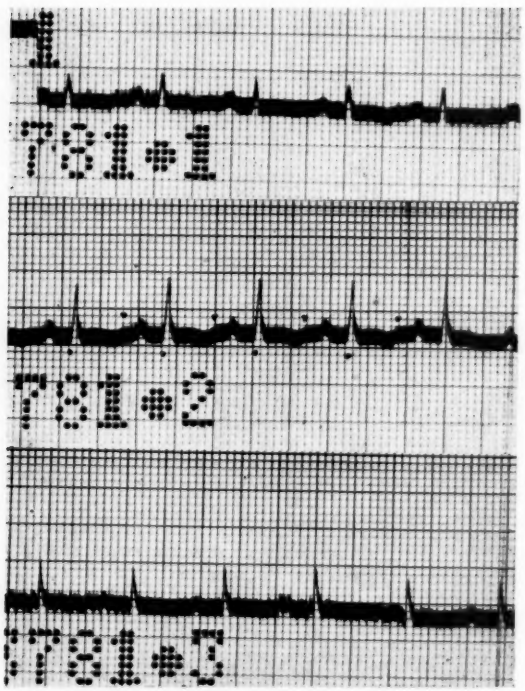

Fig. 7.—Electrocardiogram in Case 6.

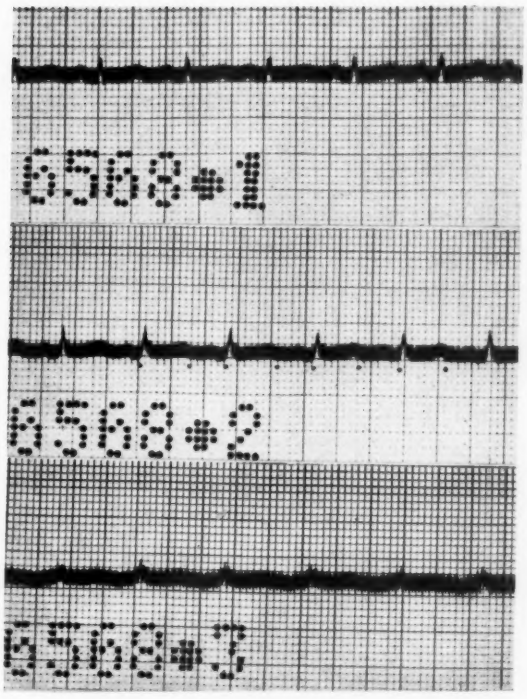

Fig. 8.—Electrocardiogram in Case 8.

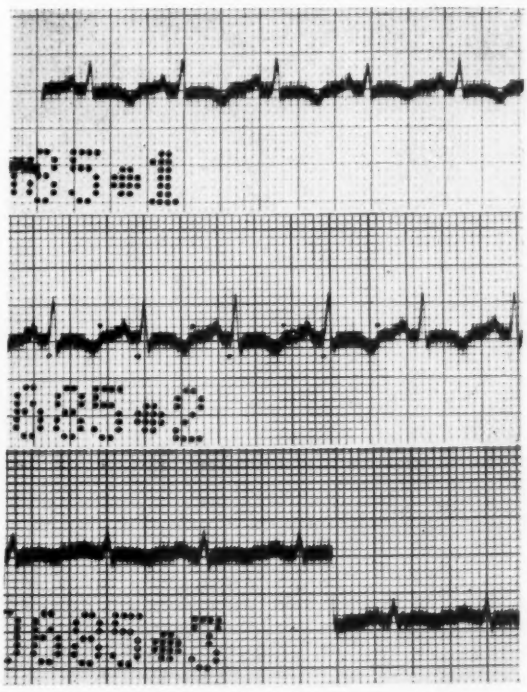

Fig. 9.—Electrocardiogram in Case 10.

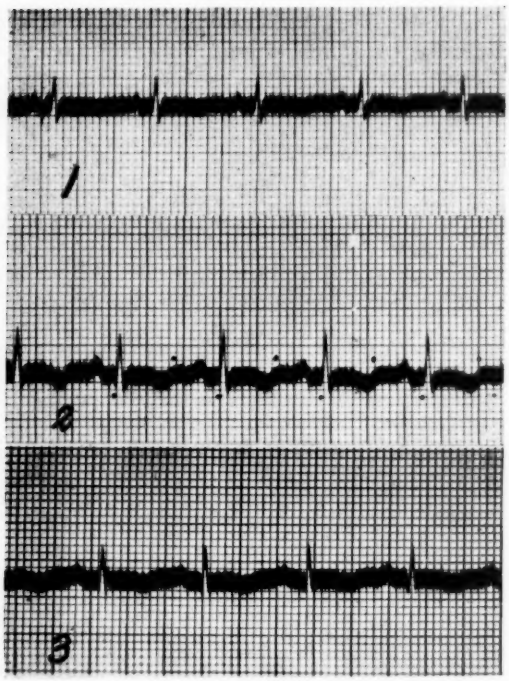

Fig. 10.—Electrocardiogram in Case 11.

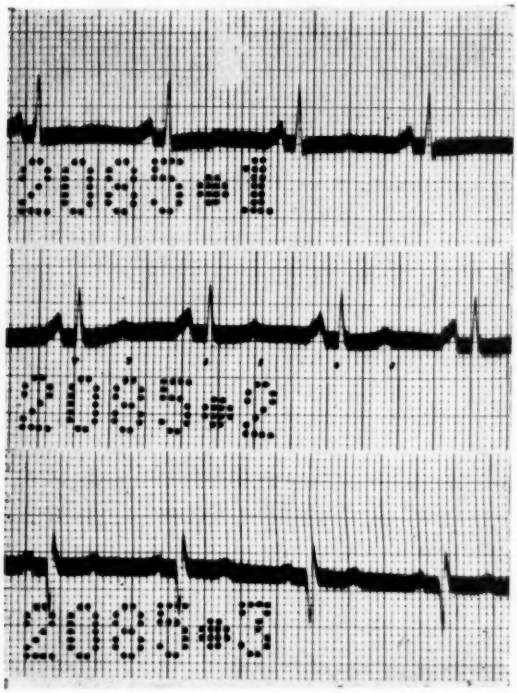

Fig. 11.—Electrocardiogram in Case 12.

for, in three patients with large pericardial effusions (as shown by paracentesis), the voltage of QRS was within the lower limit of normal, whereas in all cases there was definite abnormality of the T deflections. Sinus rhythm was present in all cases, and all but one patient had sinus tachycardia (rate above 100 per minute). The P-R interval was normal.

Special mention may be made of the study of electrical systole, or the Q-T interval, as related to the cycle, or R-R interval. The Q-T interval in each case was shorter than the predicted normal value, calculated according to Adams' formulas (mean difference, 14 per cent). Table I also gives the values of the constant K, calculated from the formula: $K = Q\text{-}T \div \sqrt{R\text{-}R}$. It will be seen that K varied from 0.344 to 0.434, with a mean value of 0.393 for the twelve male as well as the two female patients. This mean value and its range may be compared with those of the two series of normal subjects reported by Cheer and Li[12] and by Shipley and Hallaran.[21] Cheer and Li found that the average K was 0.374 in the males and 0.388 in the females, with a range between 0.348 and 0.400 for the former and between 0.355 and 0.421 for the latter. Shipley and Hallaran found that the average K was 0.397 in the males and 0.415 in the females, with a range between 0.337 and 0.433 for the former and between 0.380 and 0.456 for the latter. Thus the mean K and most of the individual values of K in the present series were well within the limits established for normal subjects by these authors. In other words, instead of having a relative prolongation of the Q-T interval, such as that which occurred in patients with congestive heart failure,[7] this group of patients with pericardial effusion and congestive failure had Q-T intervals which were somewhat shorter than normal when compared with Adams' figures, or about normal when compared with the figures given by Cheer and Li and by Shipley and Hallaran.

In the rather large literature of the electrocardiographic changes in pericardial effusion, no mention has been made as to the effect of such effusion on the Q-T duration. The fact that the duration of electrical systole is normal in patients with massive pericardial effusion which is producing signs of congestive heart failure, if confirmed, may have a theoretical interest as well as a practical value in the clinical differentiation between cardiac dilatation and pericardial effusion.

SUMMARY AND CONCLUSION

An electrocardiographic study was made of a group of fourteen patients with massive, tuberculous, pericardial effusion, the existence of which was confirmed by paracentesis or at necropsy. In all of the patients there were signs of congestive heart failure which was directly attributable to cardiac tamponade (hypodiastolic failure).

The electrocardiographic observation which was of interest in this series of cases was the fact that, taking the heart rate into consideration, the duration of electrical systole (Q-T interval) was normal. This may

aid in the differential diagnosis between marked cardiac dilatation with congestive failure and large pericardial effusion with similar congestive phenomena.

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AURICULAR FIBRILLATION IN NORMAL, INTACT ANIMALS AFTER THE INTRAVENOUS INJECTION OF MECHOLYL (ACETYL-β-METHYLCHOLINE)

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AURICULAR fibrillation in man is commonly associated with disease of the heart or the thyroid gland, and the relationship between this arrhythmia and organic disease is emphasized by clinicians. On the other hand, a large number of studies have been made[1, 2, 3, 4, 5, 6, 7, 8, 9] which show that auricular fibrillation may be produced in normal animals; in many of these, vagal stimulation was an important part of the experimental procedure. Physiologists have therefore stressed the functional origin of the arrhythmia.[6] The significance of many of these studies is, however, difficult to evaluate, for various anesthetics were used and a good deal of manipulation occurred during the experiments. Accordingly, it was considered desirable to produce auricular fibrillation by means of vagal stimulation in normal, intact, unanesthetized animals. Since the action of mecholyl reproduces the effects of stimulation of the parasympathetic nervous system,[10] this drug was chosen for the study. Although many studies on the action of mecholyl are available, there is no evidence that injection of that substance will cause auricular fibrillation in normal, intact, unanesthetized animals.

MATERIAL AND METHODS

Experiments were performed on dogs and rabbits. In every instance mecholyl* was given intravenously in doses ranging from 0.25 to 2.0 mg. for dogs, and 0.12 and 0.2 mg. for rabbits.

Ten dogs of unascertainable age and breed were used in thirty experiments; their weights ranged between 12.9 and 22.6 kilograms. No anesthesia was employed in most instances; in a few, nembutal intravenously in a dose of 25 to 35 mg. per kilogram, morphine, or ether was used. In thirteen experiments the action of mecholyl alone was studied. In seven others, which were designed to test the effect of anoxia or excess of carbon dioxide on the action of mecholyl, mixtures containing various concentrations of oxygen and carbon dioxide were given from a spirometer by inserting a soft catheter with an inflatable cuff into the trachea of the anesthetized dog. The oxygen concentrations which were used were as low as 3 per cent; the carbon dioxide concentrations varied up to 15 per cent. In one experiment, air enriched with oxygen up to 90 per cent was used. In five experiments mecholyl was given 20 to 90 minutes after the intravenous injection of ouabain in doses of 0.25 and 1.5 mg. In two experiments, five cat units of digalen were given intravenously one hour before mecholyl, and in one other experiment the mecholyl was preceded by 0.5 mg. of prostigmine subcutaneously. In one study mecholyl was given in-

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travenously to a dog which previously had received 1.0 gram of desiccated thyroid U.S.P. daily by mouth for eighteen days. Experiments were done on five rabbits whose weights ranged between 2 and 3 kg. In one dog and one rabbit the vagi were divided in the neck before the injection of mecholyl.

In one dog and two rabbits the heart was observed directly, before, during, and after the period of action of mecholyl; in these animals the chest was opened and positive pressure artificial respiration was used.

In all of the above experiments mecholyl was injected two or more times at intervals of at least ten minutes.

All studies were made by means of a vacuum tube electrocardiograph, using Lead II. Contact electrodes were used for dogs and needle electrodes for rabbits.

OBSERVATIONS

The changed heart rhythms observed in the experiments on dogs were of two general types: (1) auricular fibrillation, and (2) auriculoventricular block. Auricular fibrillation occurred at least once in seven of the ten dogs studied, but in one of them only when mecholyl was injected after a toxic dose of ouabain. Fibrillation followed twenty-nine of the sixty-seven injections of 0.5 mg. or more of mecholyl which were given to these seven dogs. Ten injections of 0.5 to 2.0 mg. of mecholyl in the three remaining dogs did not cause fibrillation of the auricles. The initial heart rate in the dogs was 100 to 130 per minute; the first change after the injection of mecholyl was usually a sinus tachycardia, which lasted one to three seconds. When fibrillation supervened it either started immediately after this tachycardia, or was preceded by a few seconds of A-V block (2:1 to 35:1). The onset of auricular fibrillation was usually characterized by a series of coarse auricular waves (Fig. 1), followed by ventricular arrest for two to eight seconds. The ventricular rate immediately after the onset of fibrillation was slow (50 to 80 per minute), and the beating was quite irregular. After fifteen to sixty seconds, however, the beating became less irregular and the rate more rapid, often reaching 300 per minute before reversion to sinus rhythm occurred. When auricular fibrillation was produced the auricular waves were at first very fine and rapid, with a frequency of approximately 1,800 per minute; thirty to ninety seconds later the auricular waves became somewhat coarser and slower. The transition to sinus rhythm was observed in one or two instances, and this occurred without any striking change in ventricular rate. Normal auricular waves appeared suddenly, and the ventricular beating became regular. The duration of the auricular fibrillation which was induced in dogs was usually from one-half to three minutes, but, in one dog, fibrillation persisted for several hours on three separate occasions. In the first instance, the arrhythmia was apparently interrupted after three hours by the injection of 1 mg. of atropine intravenously; in the second, the duration was over eight hours, and, in the third, over three hours.

*The mecholyl used in this study was supplied through the courtesy of Merck and Company, Inc.

When auricular fibrillation did not supervene, auriculoventricular block, with a ratio ranging from 2:1 to 35:1, was the usual response. At the onset of block the auricular rate often became somewhat slower than the control rate, but later often exceeded the control level. When a ventricular response occurred, the auriculoventricular conduction time was not significantly prolonged. The maximal degree of block appeared twenty to thirty seconds after mecholyl was given intravenously. This was followed by lesser grades of block, and, after thirty to ninety seconds, by sinus tachycardia of several minutes' duration.

In occasional instances other arrhythmias were observed, such as sinoauricular block, complete auriculoventricular dissociation, ventricular premature beats, and short periods of ventricular tachycardia. The P waves often became lower after the administration of mecholyl, and changes in the direction of the T waves occurred frequently. Minor alterations in the S-T segment were observed, especially when there were T-wave changes. Even when high-grade A-V block occurred, the duration of the QRS complex was not increased.

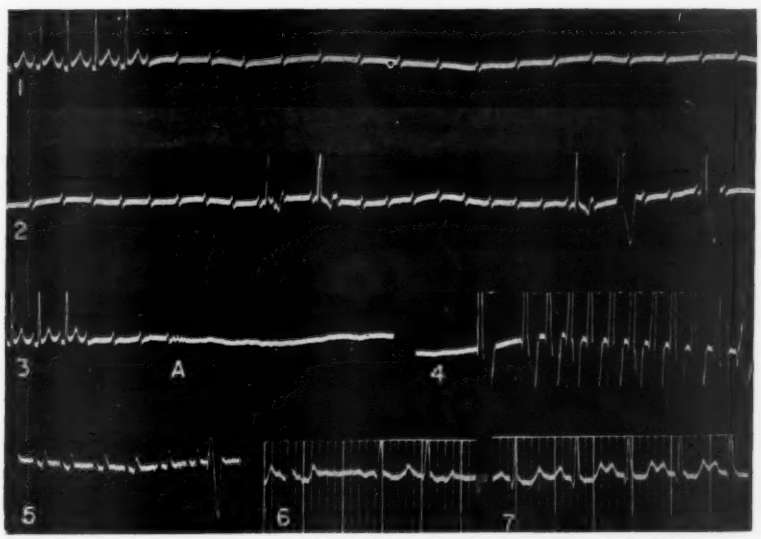

Fig. 1.—*1, 2:* Continuous tracing from dog, showing transition from sinus rhythm to high grade (26:1) block after injection of 0.75 mg. mecholyl. Note sinus slowing during period of block, and unchanged P-R interval and inverted T wave in conducted beats following block. *3-7:* Tracings from another experiment on same dog. "*A*": onset of auricular fibrillation following short period of A-V block. *4:* Twenty seconds later, showing ventricular tachycardia with continued fibrillation of auricles. *5:* Thirty seconds later. *6:* Twenty seconds later (higher film speed). *7:* Thirty seconds later, showing sinus rhythm.

In the dog in which the exposed heart was observed directly after the injection of 0.75 mg. of mecholyl intravenously, the heart stopped beating, and then dilated markedly for a few seconds. Diffuse, fine, fibrillary twitchings of the auricles ensued, followed by the onset of ventricular contractions. The fibrillary twitchings of the auricular wall

could be seen clearly because of the fact that ventricular diastole was long at the onset of fibrillation. The electrocardiogram (Fig. 2) which was taken during this experiment is typical and shows the onset of fibrillation shortly after a complex of sinus origin. After an interval

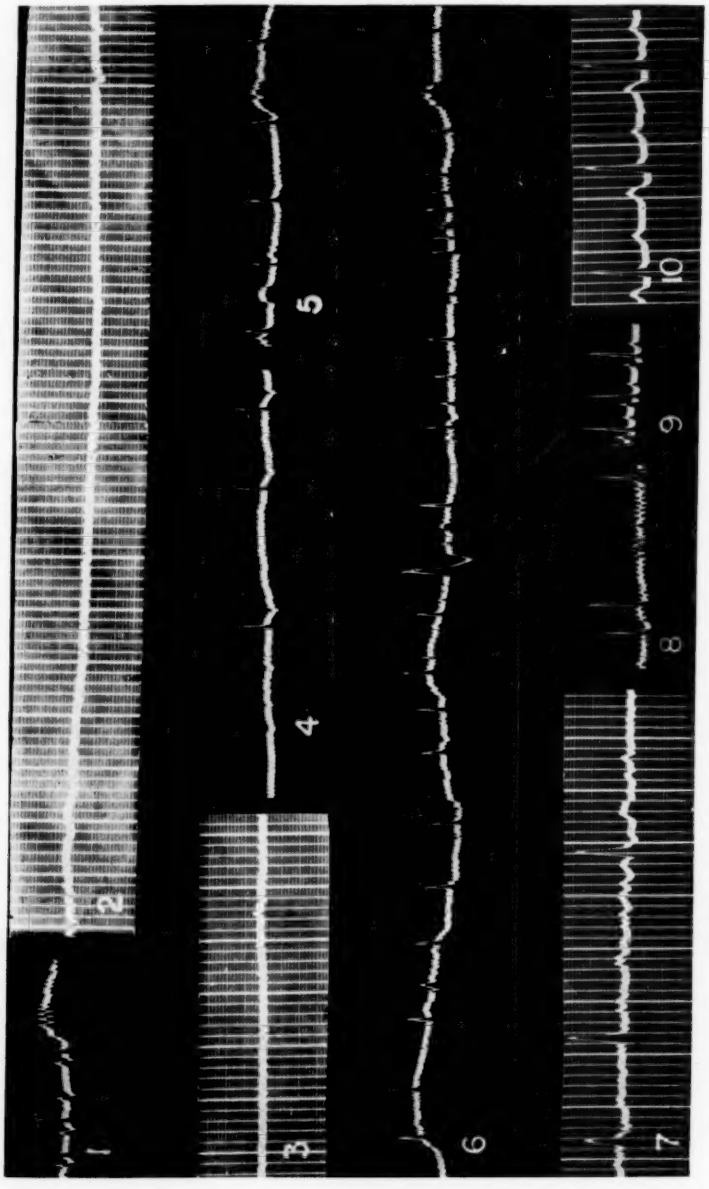

Fig. 2.—Auricular fibrillation observed in 23 kg. dog, with chest exposed, following injection of 0.75 mg. mecholyl (see text, pages 49 and 50). *1*: Transition to fibrillation. *2, 3, 4*: Consecutive strips showing sequence of events at start of fibrillation (*2* and *3* taken at higher film speed). *5*: Thirty seconds later. *6*: Fifteen seconds after "*5*." *7* and *8*: Consecutive tracings thirty-five seconds later. *9* and *10*: Show reversion to sinus rhythm ten seconds later.

of eight seconds, ventricular complexes reappear and gradually increase in rate. Toward the end of the period of fibrillation, the auricular rate decreases from the initial rate of approximately 1800 to 1200 per minute, and the fibrillary waves become coarser.

The effect on the heart of a given injection of mecholyl was unpredictable; the reaction to the same dose in a single experiment varied without apparent reason. It was consequently difficult to evaluate the action of other factors in increasing or decreasing the effect of mecholyl on the heart. However, repeated experiments adequately showed that anoxemia and excess carbon dioxide or oxygen in the ranges used did not alter the activity of mecholyl. Similarly, neither prostigmine nor thyroid, in the dosage used, affected the tendency to fibrillation or the grade of block after the injection of mecholyl. Moderate (0.25 mg.) doses of ouabain did not enhance the action of mecholyl. The action of toxic doses of ouabain was not clear-cut, although 1.5 mg. appeared to facilitate the production of fibrillation in one animal. Fibrillation occurred less frequently in animals under nembutal anesthesia than in unanesthetized animals, but ether did not interfere with the action of mecholyl. Cutting both vagi did not interfere with the production of fibrillation in the dog on which this procedure was carried out.

No dog died as a result of injecting mecholyl intravenously, although tonic convulsions of short duration, apparently associated with ventricular standstill, were noted rather frequently. Profuse salivation occurred regularly after each injection. Urination and defecation occurred infrequently, but passage of flatus was common. An increase in the depth and rate of respiration, sometimes preceded by a short period of apnea, occurred in anesthetized and unanesthetized dogs after the injection of mecholyl. The unanesthetized dogs were restless and seemed uncomfortable shortly after the injection of mecholyl, but recovery from these symptoms was rapid. Prolonged fibrillation in the dog in which it occurred was at a slow rate and without obvious symptoms, and no clinical or electrocardiographic evidence of permanent cardiac change was obtained in any of the experiments on dogs.

The results on rabbits were similar to those on dogs (Fig. 3). Fibrillation occurred in four of the five rabbits which were used, and heart block resembling that noted in dogs also occurred. Fibrillation was induced in one rabbit after cutting the vagi. In two rabbits with chest and pericardium open, fibrillation did not occur spontaneously after large doses (0.12 to 0.2 mg.) of mecholyl, although in one of these animals short periods of auricular fibrillation could be induced by pinching the auricle after the administration of mecholyl. The tracing which was taken at this time resembled those obtained when fibrillation was induced in intact rabbits. In these two animals the heart became markedly dilated after a single injection of mecholyl and did not return to its original size during the period of observation. Several rabbits died, apparently as a result of the injection of mecholyl.

DISCUSSION

There are no available previous reports of the occurrence of auricular fibrillation in normal, intact animals after the injection of mecholyl

intravenously. Cohn and MacLeod[11] observed auricular fibrillation in pithed bullfrogs, with open chest, following the administration of mecholyl intravenously, and Nahum and Hoff[12] produced that arrhythmia in dogs by the direct application of mecholyl to the auricles. Mecholyl has been injected intra-arterially in man by several observers[13, 14] who, however, have not commented on changes in cardiac rhythm. Nahum and Hoff[15] produced auricular fibrillation in patients with thyrotoxicosis by injecting mecholyl subcutaneously.

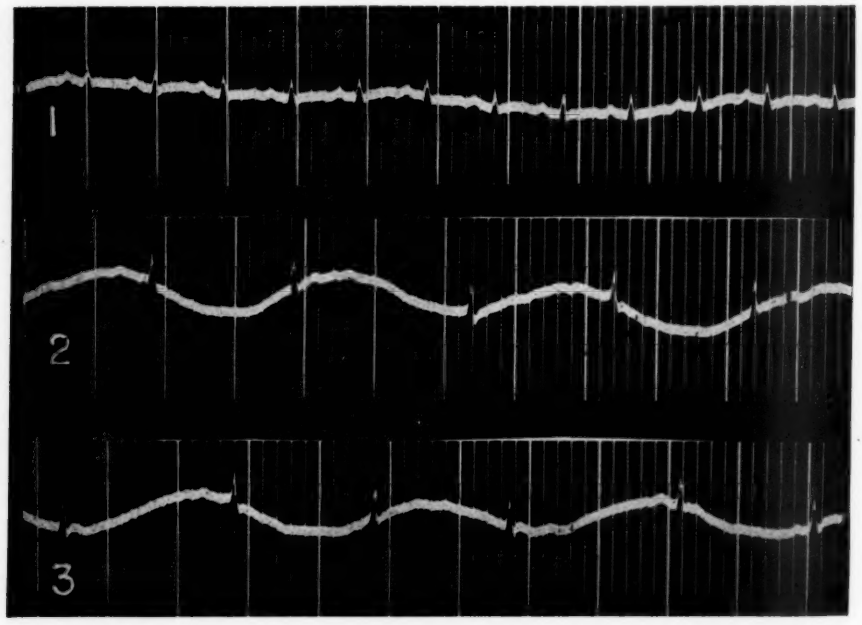

Fig. 3.—Lead II. Auricular fibrillation in rabbit after injection of 0.2 mg. mecholyl intravenously. 1 mv: 1.5 cm.; speed: 3 × normal. *1:* **Control, showing definite P waves, with regular R-R interval.** *2* **and** *3:* **Auricular fibrillation, with absent P waves and irregular ventricular beating.**

Acetylcholine, a drug which is closely related to mecholyl chemically and pharmacologically, has been shown by Goldenberg and Rothberger[7] to produce auricular fibrillation in anesthetized, vagotomized dogs when given intravenously. More recently, Noth, et al.,[16] recorded the occurrence of this arrhythmia in one dog which was given acetylcholine. Of great interest and importance are the observations of Battro and Lanari,[17, 18] who observed auricular fibrillation in three of seventeen normal human subjects after the injection of 40 mg. of acetylcholine into the carotid artery.

The action of various chemical and physical measures in facilitating or inhibiting the experimental production of auricular fibrillation has been studed by several authors. Winterberg[2] was unable to induce fibrillation by means of electrical stimulation of the vagus during asphyxia, although, after the intravenous administration of digitalis, adrenalin,

muscarine, physostigmine, and calcium salts, vagus stimulation usually produced auricular fibrillation. The results of the present study on oxygen deficiency and carbon dioxide excess corroborate his observation with regard to asphyxia. The possibility that deep nembutal anesthesia inhibits the production of fibrillation by mecholyl is interesting, for phenobarbital inhibits the production of fibrillation by direct electrical stimulation of the heart,[8] and sodium amytal prevents fibrillation in rabbits after the injection of calcium chloride.[23] The results of Winterberg[2] and Pines[24] suggest that ouabain and prostigmine might increase the tendency to fibrillation, and the clinical observations of Nahum and Hoff[15] indicate that thyroid feeding might have the same action. Although these drugs were administered in adequate doses[25, 26] in our experiments, no striking effect was noted. Since the present experiments deal with a drug which produces locally most of the changes brought on by peripheral stimulation of the vagus, the production of fibrillation by mecholyl in animals with cut vagi is not significant, except to suggest that the action of the drug is not central, but local.

Auricular fibrillation has been produced experimentally in animals by a variety of chemical substances.[2, 6, 7, 8, 9] Many of these act through the vagus either directly or reflexly, and others have a vagal action in themselves. However, a number of substances with no such action, such as ether, ethyl alcohol, carbon monoxide, arsenic, hydrogen sulfide, and aspirin, have been reported to cause auricular fibrillation in human subjects with normal hearts.[27] It appears, therefore, that a variety of chemical agents may cause auricular fibrillation. Nevertheless, the close relationship of mecholyl to acetylcholine, the vagus hormone, cannot be minimized.

Changes in the form of the electrical complex were not analyzed in detail in the present study because only one lead was used and because several reports on the changes produced in the human electrocardiogram by mecholyl are available.[19, 20] It is of interest, however, that several of the obvious abnormalities in our tracings, i.e., S-A block, A-V block, small P waves, and changes in the T waves, were observed by Einthoven,[21] in 1908, after electrical stimulation of the vagus nerve in dogs. Our observations on the production of auricular fibrillation in general are also in close agreement with those of other workers who have used other methods to induce this arrhythmia. Almost every available discussion[6] of the subject comments, either expressly or by implication, on the inexplicable variability in the response to a given stimulus, even in the course of a single experiment. The variability in the duration of the auricular fibrillation, once it has been produced, has also been frequently observed. The occurrence of fine, rapid, auricular waves at the start of the fibrillation, which gradually become coarser, has been noted when direct electrical stimulation of the auricle was the means used to initiate fibrillation.[1, 22] It has been shown, however, that vagus stimula-

tion when the heart is already fibrillating increases the rate and decreases the amplitude of the auricular waves.[4, 22] Thus the change in the rate and amplitude of the fibrillary waves which was observed in the present study may have been the result of a progressive decrease in the action of the injected mecholyl.

Physiologists had realized that vagus stimulation produces conditions which are favorable for the production and maintenance of auricular fibrillation, even before the careful study of this problem by Winterberg,[1] in 1907. His observation that faradic stimulation of the vagi facilitated the production of auricular fibrillation by direct electrical stimulation of the auricle, and that vagal stimulation also increased the duration of fibrillation after cessation of local stimulation was confirmed in 1913 by Robinson.[4] That auricular fibrillation may be produced by vagus stimulation alone has been claimed by several workers.[3, 4, 5, 28, 29] The earlier experiments were criticized by Winterberg because they dealt with abnormal conditions, as, for instance, a myocardiograph or electrode in contact with the auricle. It is not clear from the protocols of later workers whether or not this source of error has been avoided, but, in any case, the occurrence of auricular fibrillation in normal hearts after vagal stimulation alone must be exceedingly infrequent. Since mecholyl is a synthetic chemical which is not normally present in the body, the results of the present study cannot be interpreted as evidence favoring the possibility that fibrillation may be produced by vagal stimulation alone, although they do re-emphasize the close relationship between that arrhythmia and the vagus nerve. The possible relationship of vagal stimulation to spontaneous auricular fibrillation in man has been suggested by clinical studies,[30] as well as by experimental observations.[15, 17, 18]

SUMMARY AND CONCLUSIONS

1. Auricular fibrillation and heart block were produced in intact and unanesthetized dogs and rabbits by the intravenous injection of mecholyl.

2. Anoxemia, excess carbon dioxide and oxygen, desiccated thyroid, and ouabain did not appear to alter the effect of mecholyl on the cardiac mechanism.

3. The relation of vagal stimulation to auricular fibrillation is discussed.

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COR PULMONALE: OBSERVATIONS IN FIFTY AUTOPSY CASES

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ONE of the less common etiologic types of heart disease is that which is associated with certain chronic lung affections, notably chronic pulmonary emphysema, and variously called cor pulmonale, emphysema heart, or pulmonary heart disease. Although it is recognized as a distinct entity, there is some difference of opinion regarding its frequency. Particularly conflicting are the present views concerning the role played by chronic lung disease in its etiology.

The common post-mortem occurrence of right ventricular hypertrophy and chronic emphysema, as recorded in past writings, led to the time-honored conception that the narrowing thrombosis and destruction of pulmonary capillaries in emphysema elevated the pulmonary pressure and burdened the right ventricle, which underwent dilatation and hypertrophy and ultimately failed. This explanation of the relation between chronic emphysema and heart disease was accepted by most clinicians and pathologists of a generation ago. Recent observers, however, have questioned the relation of chronic emphysema to right-sided heart failure. White and Bremer,[1] for example, have stated: "A true cor pulmonale (or pulmonary heart disease) is distinctly rare; it is present in certainly not much over 1 per cent of patients with heart disease," and, in the same article, they said: "Ordinarily, asthma, emphysema, and pulmonary tuberculosis, even though of high degree, do not produce cor pulmonale."

From the roentgenologic observations on the heart in eighty cases of chronic emphysema, Parkinson and Hoyle[2] said: "Cardiac failure from emphysema alone is surprisingly rare," and "Such cardiac signs and symptoms as may appear in emphysema are more likely due to hypertension than to the direct effect of emphysema on the heart."

The most extensive work on the subject of emphysema in the past decade, at least in America, is that of Alexander, Kountz, and their associates, but their conclusions further emphasize the present confusion regarding the relation of emphysema to heart disease, and, particularly, to the so-called cor pulmonale. In one of their earlier articles[3] on the effects of long-standing bronchial asthma on the heart, they said: "The impression is gained that, as a rule, the heart remains singularly free from injury after continuous bronchial asthma despite the attendant emphysema," and two years later[4] they stated: "It is believed that,

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despite peripheral signs which simulate decompensation, advanced emphysema does not necessarily affect the heart." As recently as 1934, in an extensive review of emphysema,[5] Kountz and Alexander stated: "The preponderance of evidence points to the fact that there is no cardiac lesion in the majority of cases of emphysema." Just two years later[6] they exactly reversed their opinion and said: "From these observations it appears that the heart is affected in the majority of patients with emphysema." In the light of such contradictory statements on the relation of emphysema to heart disease, further study of the problem seems timely.

The clinical recognition of cor pulmonale before the advent of congestive failure is extremely difficult and often impossible, because symptoms such as dyspnea, orthopnea, and cough are often caused by the accompanying chronic lung disease, and there may be little or no objective evidence implicating the heart. Furthermore, patients with emphysema and other chronic lung affections are usually beyond forty years of age, and, if they are observed during a period of congestive failure, it may be impossible to evaluate the influence of such factors as hypertension and coronary artery disease. Symptoms directly attributable to cor pulmonale appear only after the heart begins to fail, and most of the patients never recover from their first breakdown. It is apparent, therefore, that the clinical recognition of cor pulmonale or the emphysema heart is fraught with much uncertainty, and that conclusions regarding its incidence and the role that chronic lung disease may play in its etiology must depend for their validity upon evidence afforded by postmortem study.

This paper deals with observations on fifty cases which we believe to be examples of cor pulmonale. They occurred in a series of 6,548 consecutive autopsies which were performed at the Cleveland City Hospital during the past ten years, and constitute 6.3 per cent of 790 autopsied patients who died of heart disease.

CRITERIA FOR THE ANATOMIC DIAGNOSIS OF COR PULMONALE

Examples of right ventricular hypertrophy secondary to mitral valve disease were easily excluded. Realizing that the commonest cause of right ventricular hypertrophy is left ventricular strain, we naturally excluded all cases of aortic valve disease, and those in which there was a significant degree of coronary artery disease. In none of the cases had hypertension been present; furthermore, a careful study of the kidney vessels was made, and no cases in which there was significant renal vascular disease were included.

As we possess no means of measuring the pulmonary blood pressure in man, the only available index of right-sided heart strain is hypertrophy and dilatation of the right ventricle. The thickness of the ventricular wall was used as a criterion of hypertrophy, and only cases in which the right ventricle measured 5 mm. or more were included. This procedure,

of course, does not give information concerning the weight of the right ventricle, because no account is taken of the factor of dilatation. On the other hand, it seems fair to assume that a right ventricle which measures 5 mm. or more is the seat of hypertrophy, and that, by using this criterion, one underestimates rather than overestimates the actual hypertrophy.

Except for two cases in which there was marked compression of the pulmonary artery by an aneurysm at the root of the aorta, all of the patients in this series had advanced lung disease. The incidence and types of lung disease which were observed are shown in Table I.

TABLE I

COR PULMONALE IN RELATION TO LUNG DISEASE IN FORTY-EIGHT AUTOPSY CASES

LUNG DISEASE	NO. OF CASES
Chronic emphysema	32
Emphysema with conglomerate silicosis	7
Emphysema with ulcerative tuberculosis	5
Emphysema with fibroid tuberculosis	1
Emphysema with silicotuberculosis	1
Conglomerate silicosis	1
Pulmonary fibrosis	1

In thirty-two cases the lungs showed the changes characteristic of chronic emphysema, together with varying grades of bronchitis, bronchiectasis, and fibrosis. In fourteen instances emphysema was accompanied by ulcerative or fibroid tuberculosis, silicosis, or silicotuberculosis, and, in one case, advanced conglomerate silicosis was the only significant pulmonary lesion. Finally, there was one example of severe bilateral fibrosis of the lungs which was thought, but not proved, to have been caused by syphilis. This case was that of a 29-year-old negress who had a positive blood Wassermann reaction, and had exhibited clinically the cardinal signs and symptoms of right-sided heart failure.

Reference to Table II shows that the heart in the majority of the cases was overweight; in only eleven instances did it weigh less than 400 grams. In twenty-five instances the heart weighed from 400 to 500 grams, and, in fourteen cases, more than 500 grams. No strict correlation between the thickness of the walls of the two ventricles was observed, although, when the right ventricular hypertrophy was extreme, the wall of the left ventricle was thickened in all but one case (W. B., Autopsy No. 9035, in which the walls of both chambers measured 12 mm.).

The degree of right-sided hypertrophy, as indicated by the thickness of the wall of the right ventricle, fell within fairly narrow limits in the majority of cases. For example, in forty-one, or 80 per cent, the right ventricle measured from 5 to 8 mm. In two cases it was 9 mm.; in three, 10 mm.; in one, 11 mm.; in two, 12 mm., and in one, 14 mm. in thickness. Thus, in a few cases, the right ventricular hypertrophy became extreme, but most of the patients succumbed before the right ventricle attained a thickness of more than 8 mm. In two clear examples of in-

creased pulmonary pressure and right-sided heart failure, uncomplicated by lung disease (S.W., Autopsy No. 7102, and H.H., Autopsy No. 11946), in which the pulmonary artery was compressed by an aneurysm at the root of the aorta, the wall of the right ventricle measured 7 mm. in thickness.

Varying grades of left ventricular hypertrophy were observed in the majority of cases; in thirty, or 60 per cent, the left ventricular wall measured 15 mm. in thickness, and in forty-five, or 90 per cent, the left ventricle was 12 mm. or more in thickness. The cause of this rather consistent hypertrophy of the left ventricle is not clear. It could not be ascribed to increased work per se, for every effort was made in this series of cases to exclude factors which burden the left ventricle, i.e., hypertension and aortic valve disease. Neither could it have been the result of coronary disease, for no heart which showed significant changes in the coronary arteries was included in this study. Perhaps the anatomic relation of the two ventricles is such that hypertrophy of one ultimately involves the other. If this be true, it may account, in part, at least, for the frequent occurrence of right ventricular hypertrophy in cases of primary left ventricular strain. For example, hypertrophy of both ventricles is found at autopsy in cases of chronic hypertension in which the patients died of a cerebral accident but never had clinical evidence of left ventricular failure. Obviously, the hypertrophy of the right ventricle in such cases cannot be ascribed to backward failure of the left ventricle.

CLINICAL OBSERVATIONS

The clinical observations in the majority of the cases here recorded were not complete because thirty-five, or 70 per cent, of the patients had advanced congestive failure at the time of admission to the hospital and died within seventy-two hours. The most outstanding features of the clinical course in this group were (1) the relatively short duration and progressive nature of the symptoms of right ventricular failure, and (2) the fact that forty-three, or 86 per cent, died of their first attack of cardiac failure.

Age.—The majority were over 50 years of age. In the group of thirty-two cases in which emphysema was the major lung disease, one patient was 35 years of age, ten were between 40 and 50, 12 were between 50 and 60, and 9 were over 60.

Sex.—All but two of the patients were men.

Place of Birth.—Excluding two cases of pulmonary artery compression from aneurysms and one of extensive pulmonary fibrosis probably caused by syphilis, thirty-two, or 68 per cent, of the patients were foreign born, and most of these were from Southeastern Europe.

We have felt for some time that there was a higher incidence of chronic pulmonary emphysema in the peasant class of Southeastern Europe than in similar classes from other parts of the world, and, in this connection,

TABLE II

CLINICAL AND AUTOPSY DATA IN FIFTY CASES OF COR PULMONALE

NAME	AGE	SEX	COLOR	EKG AXIS DEVIATION	AUTOPSY NO.	LUNGS	HEART WEIGHT GM.	THICKNESS RIGHT VENTRICLE MM.	THICKNESS LEFT VENTRICLE MM.
S.C.	52	M	W	--	6548	Emphysema	400	7	15
A.R.	55	M	W	--	6852	Emphysema	520	7	15
W.F.	57	M	W	R.A.D.	7080	Emphysema, Ulcerative Tuberculosis	500	8	17
M.O.	60	M	W	--	7304	Emphysema, Conglomerate Silicosis	550	6	15
A.K.	56	M	W	R.A.D.	7365	Emphysema	600	6	15
J.B.	56	M	W	R.A.D.	8039	Emphysema, Bronchiectasis	500	9	20
J.C.	47	M	B	--	8872	Conglomerate Silicosis	350	6	12
W.B.	59	M	B	--	9035	Emphysema, Bronchiectasis	300	12	12
J.H.	49	M	W	--	9043	Emphysema	380	14	18
F.G.	47	M	W	--	9062	Emphysema	500	9	15
A.C.	54	M	W	R.A.D.	9238	Emphysema	350	8	20
A.H.	59	M	W	--	9131	Emphysema	500	10	20
W.G.	67	M	W	--	9195	Emphysema	400	8	17
T.S.	35	M	W	--	9282	Emphysema	500	6	13
N.K.	50	M	W		9471	Emphysema	450	8	14
A.B.	48	M	B	--	9709	Emphysema	450	12	20
L.P.	48	M	W	R.A.D.	9803	Emphysema	580	6	15
G.L.	56	M	W	--	10098	Emphysema	350	7	14
M.B.	52	M	W		10131	Emphysema, Bronchiectasis	350	5	10
A.D.	58	M	W	--	10142	Emphysema	420	5	11
J.K.	42	M	W	R.A.D.	10321	Emphysema, Ulcerative Tuberculosis	550	5	13
E.M.	45	M	W	--	10510	Emphysema	450	6	19
J.S.	50	M	W	--	10538	Emphysema, Silicotuberculosis	550	5	14

J.M.	40	M	W	--	10679	Emphysema, Conglomerate Silicosis	500	5	15
O.S.	73	M	W	--	10904	Emphysema	530	6	13
A.S.	29	F	B	L.A.D.	11898	Extensive Fibrosis	250	7	17
W.S.	65	M	W	--	11993	Emphysema, Conglomerate Silicosis	420	8	15
T.O.	62	M	W	--	11967	Emphysema	400	7	11
W.C.	61	M	W	R.A.D.	11919	Emphysema, Tuberculosis	420	8	15
S.S.	64	M	W	--	11996	Emphysema, Bronchiectasis	450	6	12
W.T.	48	M	W	R.A.D.	12159	Emphysema	720	11	16
J.C.	61	M	W	--	12161	Emphysema, Conglomerate Silicosis	500	8	20
J.B.	63	M	W	N.A.D.	12184	Emphysema	420	7	15
A.H.	63	M	W	L.A.D.	11466	Emphysema, Bronchiectasis	400	6	15
M.E.	43	M	W	R.A.D.	12329	Emphysema	600	7	18
H.A.	51	M	W	R.A.D.	11930	Emphysema	400	8	15
F.V.	50	M	W	R.A.D.	12540	Emphysema	375	8	10
M.S.	52	M	W	R.A.D.	11978	Emphysema, Bronchiectasis	450	5	13
F.M.	65	M	W	--	11837	Emphysema	550	10	15
A.Z.	49	F	W	--	11525	Emphysema	400	6	12
C.M.	52	M	W	N.A.D.	12574	Emphysema, Conglomerate Silicosis	350	6	12
M.R.	70	M	W	L.A.D.	12833	Emphysema, Bronchiectasis	675	6	12
J.H.	67	M	W	--	12878	Emphysema, Conglomerate Silicosis	390	5	14
S.B.	54	M	W	--	13021	Emphysema, Tuberculosis	530	8	15
W.G.	69	M	W		12918	Emphysema, Tuberculosis	525	5	16
M.V.	52	M	W	R.A.D.	12925	Emphysema, Conglomerate Silicosis	460	8	10
E.B.	77	M	W	--	12704	Emphysema	520	7	18
W.T.	45	M	W	R.A.D.	12176	Bilateral Fibroid Tuberculosis, Emphysema	300	10	15
S.W.	42	M	B	R.A.D.	7102	Normal	400	7	13
H.H.	60	M	W	--	11946	Normal	420	7	15

it is interesting that Cleveland has, relative to the total population, a larger number of immigrants from Southeast Europe than eight other large American cities, as shown in Table III. This fact probably has some bearing on the high incidence of cor pulmonale at the Cleveland City Hospital.

TABLE III

PERCENTAGE OF TOTAL POPULATION REPRESENTED BY PERSONS BORN IN SOUTHEAST EUROPE IN NINE UNITED STATES CITIES IN 1930*

CITY	POPULATION	FOREIGN BORN	PERCENTAGE FOREIGN BORN
New York	6,930,446	275,570	3.98
Chicago	3,376,438	116,013	3.44
Philadelphia	1,950,961	30,710	1.57
Detroit	1,568,662	39,941	2.55
Cleveland	900,429	85,540	*9.50*
Baltimore	804,874	6,058	0.75
Boston	781,188	2,803	0.36
Pittsburgh	669,817	18,706	2.79
Buffalo	573,076	6,028	1.05

*For these data we are indebted to Mr. Howard Whipple Green, Secretary of the Cleveland Public Health Council.

Symptoms and Signs.—Even in those cases in which a reliable history was obtained, it was not always possible to distinguish cardiac symptoms from those caused by the associated pulmonary disease. Cough, dyspnea on exertion, and cyanosis, with some limitation in capacity to exercise, were the usual complaints, and had often continued for several years, whereas the signs of right ventricular failure—venous distention, hepatic enlargement, edema, and ascites—rarely lasted longer than six to eight months. Until the appearance of such signs there was no clear evidence to incriminate the heart. A history of effort angina was obtained in only one instance, and this occurred in a case of syphilitic aortic aneurysm which compressed the pulmonary artery. Four patients had noted substernal pain, and four complained of precordial pain after coughing. Varying grades of dyspnea were observed in every case, and orthopnea was present in all but four patients. Respiratory distress was an outstanding feature, and, unlike that observed in the usual case of left ventricular failure, periodic breathing of the Cheyne-Stokes type and attacks of nocturnal dyspnea (cardiac asthma) were rarely seen. For example, Cheyne-Stokes breathing was observed in two, and nocturnal dyspnea in four, cases.

Cyanosis, like dyspnea and orthopnea, was conspicuous, and often advanced to an extreme grade as the heart failure increased. In all but three cases, distention of the neck veins and hepatic enlargement were noted clinically. Ascites was present in fifteen cases and general anasarca in sixteen. An erythrocyte count was done in thirty-two cases, and in twenty-one of these the cells numbered more than 5,000,000. The highest count observed was 7.9 million, and in this case, before the onset of congestive failure, a diagnosis of polycythemia vera had been made in another hospital. In twenty cases an electrocardiogram was obtained;

it showed right axis deviation in fifteen cases, no deviation in two, and left axis deviation in three cases.

Unfortunately, many patients in this series were so ill at the time of admission and failed so rapidly that satisfactory roentgenologic studies were not possible. In ten out of nineteen cases in which roentgenologic studies were made, the roentgenologist reported enlargement of either the conus pulmonalis or the body of the right ventricle.

SUMMARY

The observations made in this series of cases entirely support the conclusions of older clinicians and pathologists regarding the relation between chronic emphysema and failure of the right side of the heart. The clinical course and autopsy observations indicate that the right ventricle is burdened in emphysema, presumably by an elevation in pulmonary pressure, and that it undergoes dilatation and hypertrophy and ultimately fails. That increased pulmonary pressure burdens the right ventricle and leads ultimately to death from heart failure is shown clearly by two cases in this series in which an aneurysm at the root of the aorta compressed the main pulmonary artery.

In the majority of cases the left ventricle also was hypertrophic, but the cause of this hypertrophy was not apparent. It is suggested that the anatomic relation of the two ventricles is so intimate that hypertrophy of one chamber ultimately involves the other.

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THE OCCURRENCE IN ANGINA PECTORIS OF ELECTROCARDIOGRAPHIC CHANGES SIMILAR IN MAGNITUDE AND IN KIND TO THOSE PRODUCED BY MYOCARDIAL INFARCTION*

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DURING the last few years we have observed a number of cases of angina pectoris in which electrocardiograms obtained during paroxysms of substernal distress, either spontaneous or induced, have shown striking changes in the form of the ventricular complex comparable in magnitude and similar in kind to those which occur during the first few hours following the sudden occlusion of a large coronary artery. We would like to present here our clinical and electrocardiographic observations in five such cases, and to make a few comments with reference to their interpretation.

CASE 1.—Mr. L. E. T., an American office worker, aged 35 years, was first seen on Feb. 2, 1935. Early in the summer of 1934, while playing golf, he noticed pain on the ulnar side of the left arm which disappeared promptly when he rested. In subsequent attacks the pain began under the middle and upper sternum and radiated to the left arm as its intensity increased. The distress invariably disappeared within two minutes when he stopped exercising. Walking, climbing stairs, and lifting were the types of effort which most frequently caused pain. The symptoms were most likely to develop on exertion in the cold, or on exertion soon after a meal. The pain was severe but dull, and was accompanied by a sensation of fullness. There was no history of rheumatic fever or diphtheria. When he was 17 or 18 years of age, the patient had a penile lesion which was not followed by a skin rash. No antisyphilitic treatment was administered. In 1917 he had had intestinal obstruction, but recovered without an operation.

On examination there was no enlargement of the heart, but a very faint aortic diastolic murmur was audible along the left border of the sternum when the breath was held after forced expiration. There was slight accentuation of the aortic second sound. The blood pressure was 125/70. The remainder of the physical examination was entirely negative. The Kahn test was strongly positive, and a diagnosis of angina pectoris due to syphilitic aortitis, with obstruction of the coronary orifices, was made.

The electrocardiogram (Fig. 1*A*) showed slight left axis deviation, not outside normal limits, and a heart rate of 88 per minute. After exertion sufficiently severe to induce mild anginal pain (Fig. 1*B*) the heart rate was approximately 130 per minute, and the electrocardiogram showed pronounced downward displacement of the RS-T junction in Lead II and less marked RS-T displacement in the same direction in Leads I and III. In Lead I, in which the T wave was originally sharply upright,

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this deflection was flat or slightly inverted. In addition to these changes in the final ventricular deflection, there was a striking increase in the size of the S deflection in Leads II and III.

Nitroglycerine and aminophyllin were prescribed, and the patient reported on Feb. 25 that he was still having attacks, but that they were much less frequent and of shorter duration than formerly. Between Feb. 16, 1935, and April 10, 1935, eight intramuscular injections of bismuth salicylate (2 gr.) were given, and soon after these injections were begun, the patient stated that there was a slight increase in the severity of his symptoms.

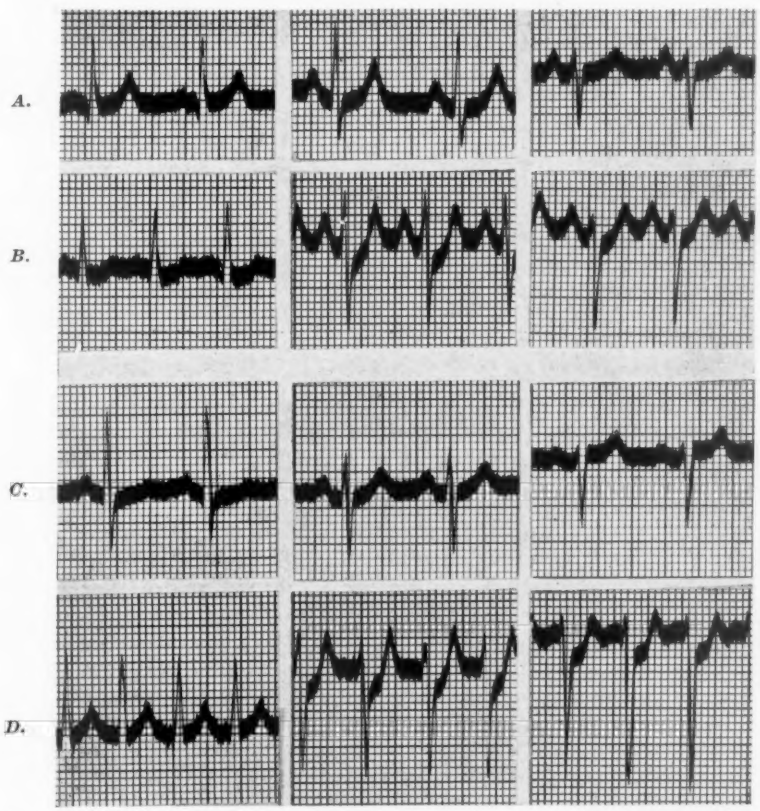

Fig. 1.—*A*, Case 1. Control electrocardiogram. *B*, Case 1. Electrocardiogram taken after exertion sufficiently severe to induce mild substernal distress. *C*, Case 2. Control electrocardiogram. *D*, Case 2. Electrocardiogram taken during a mild paroxysm of anginal pain induced by exertion. (Reproduced by courtesy of the Macmillan Company.)

On May 14, 1935, the patient's wife reported that he had died on May 4. On this date he went to the assistance of a woman who had fallen and broken her leg. The effort and excitement were promptly followed by a severe attack of chest pain, accompanied by dyspnea. These symptoms persisted until death a few hours later.

Case 2.—Mr. O. S. G., a gas station attendant, 46 years old, was first seen on Feb. 27, 1928. At that time he was complaining of headache, shortness of breath, giddiness, and a sense of oppression beneath the sternum. He had been having headaches in the occipital region on the right side for eight or nine years, but they had been severe for only two years. The dyspnea, which occurred only on exertion,

and giddiness had been troublesome for one year. The substernal discomfort had occurred on two occasions only and consisted in a burning sensation beneath the surface of the chest. There was a history of gonorrhea many years before, and of three attacks of pneumonia within the preceding nine years.

On examination the heart was borderline in size, and no murmurs were heard. The aortic second sound was somewhat accentuated. The blood pressure was 216/146. The electrocardiogram showed slight left axis deviation. The patient was seen again on Aug. 26, 1929. At this time he stated that after his first visit he did not improve. The basal metabolic rate was measured elsewhere and was reported to have been plus 38 per cent. The administration of iodine and x-ray irradiation of the thyroid gland were followed by improvement, and he was able to return to work. Two weeks before this second visit he began to have attacks of rapid heart action. A tentative diagnosis of paroxysmal tachycardia was made at this time. The blood pressure was 140/80. The basal metabolic rate was -1 per cent.

The patient was seen for the third time on Jan. 15, 1935. He stated that for approximately two years he had felt fairly well, except that during the preceding four or five weeks he had begun to have a burning sensation beneath the upper sternum. This was associated with eructations of gas, but he did not feel distended. This sensation frequently occurred at night. He thought it was often brought on by exertion, but it sometimes lasted for fifteen minutes even if he remained quiet. He could sometimes walk a considerable distance without trouble, but one severe attack was brought on by shoveling snow, and he remained in bed for two days after this. The burning sensation was accompanied by constriction, and radiated to the ulnar side of the left arm.

The heart was not enlarged at this time, either to physical or roentgenologic examination. The aortic second sound was markedly accentuated. No murmurs were heard. The blood pressure was 210/125.

The electrocardiogram (Fig. 1*C*) which was taken while the patient was at rest showed slight left axis deviation, but was not outside normal limits. The heart rate was approximately 94 per minute. Following exertion sufficiently severe to induce mild substernal distress (Fig. 1*D*), the heart rate was 180 per minute, and there was pronounced downward displacement of the RS-T junction and segment in Leads II and III of the electrocardiogram. In addition, there were a very conspicuous change in the form of the T deflection in Lead I and a great increase in the size of the S deflections in Leads II and III. The P wave was not distinctly visible, but was apparently superimposed upon the end of the T deflection of the previous cycle because of the rapid heart rate and a slight prolongation of the P-R interval. Extrasystoles were noted after the exercise test, but were not recorded. About one-half hour later, shortly after an orthodiagraphic examination of the heart, the patient was found lying on the floor in one of the dressing rooms of the Department of Roentgenology. He was unconscious, pulseless, and extremely cyanotic, and was making gasping respiratory movements. He could not be revived.

CASE 3.—F. L. K., a physician, aged 66 years, was seen on Dec. 9, 1937. He stated that he had been well until the latter part of October of that year, when he began to have anginal pain. The first attack occurred while he was driving his car, and lasted about fifteen minutes. After this, exertion and excitement frequently induced attacks, and nocturnal attacks often awakened him from sleep. Cold increased the tendency to paroxysms. The pain was felt first in the muscles below and above the elbow joint, was bilateral, and was perhaps more severe on the right side. After it began in the arms, it was felt in the mid-chest on both sides of the sternum, but more on the left. It spread to the neck, jaws, and teeth, and even to the top of the head and as low as the waistline. It consisted in severe aching, with pressure and constriction. The longest attack lasted twenty minutes.

Nitroglycerine gave prompt relief. The first effect of this drug was to cut down the peaks of the waves of pain. The patient did not use tobacco. He said that his blood pressure had been a little high since his student days.

He was distinctly overweight. The heart was not enlarged. There was a faint, late, systolic murmur at the apex. The blood pressure was 160/98. The remainder of the examination was negative.

An electrocardiogram was taken, and this procedure was immediately followed by a spontaneous attack of angina. The first curve (Fig. 2*A*) shows slight left axis deviation, with partially inverted T deflections in Lead I and slight flattening of the RS-T segment in Leads II and III. The electrocardiogram which was taken at the height of the attack (Fig. 2*B*) shows pronounced downward displacement of the RS-T junction and segment and definite changes in the QRS complex, consisting in the development of a prominent S deflection in Lead II and a pronounced increase in the size of the S deflection in Lead III. The heart rate rose from approximately 70 per minute before the attack to approximately 100 per minute when the distress was at its height. In a later and similar spontaneous attack there was a rise in the systolic blood pressure from 160 mm. Hg to 180 mm. Hg. After nitroglycerine the pain subsided promptly (Fig. 2*C*), and the electrocardiogram regained its original form within fifteen minutes (Fig. 2*D*).

The patient died suddenly about one week after these observations were made.

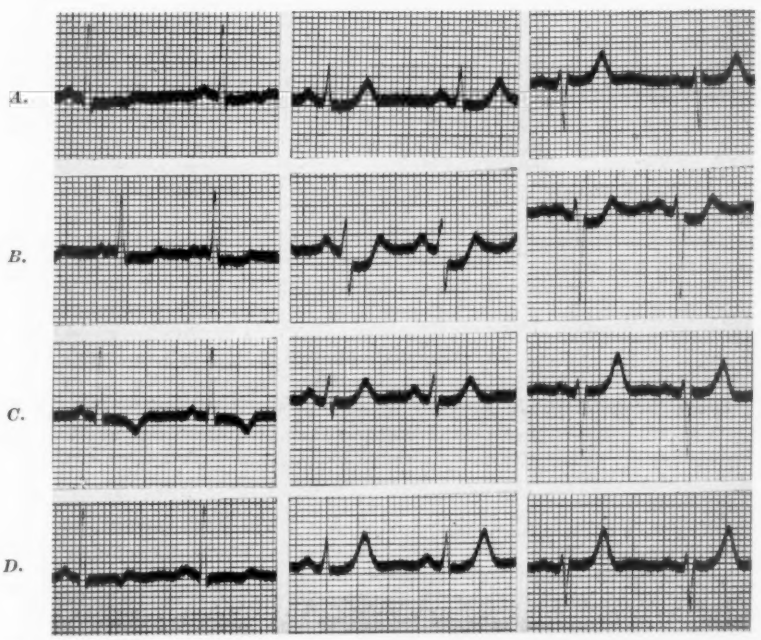

Fig. 2.—Case 3. *A*, Control electrocardiogram. *B*, Taken during a spontaneous attack of anginal pain. *C*, Taken five minutes after *B*, following the administration of nitroglycerine (1/100 gr.). *D*, Taken ten minutes after *C*.

CASE 4.—Mr. T. McL., an electrical engineer, was first seen at the University Hospital on June 1, 1927. At this time he was complaining of epigastric pain which occurred two to three hours after meals. This distress was of three years' duration. A clinical diagnosis of peptic ulcer was made, and evidence of duodenal ulcer was discovered on roentgenologic examination. A suitable diet and alkaline powders were prescribed. The patient was not seen again until Dec. 5, 1938, when

he was admitted to the hospital. At this time he was 42 years of age. He stated that the gastric symptoms had eventually disappeared, and that he had been well until November, 1937, when he began to experience sharp, excruciating pain in the precordial region, with radiation to the left arm. These attacks of pain were precipitated at first by heavy lifting, and later by walking. They became more frequent and more severe until May, 1938, when the patient consulted a physician and was put to bed and told to reduce his consumption of tobacco to six or seven cigarettes per day. He had been in the habit of smoking twenty or more cigarettes daily. After he had been in bed for two days, the attacks ceased. He remained in bed for six weeks. After this he gradually increased his activity, and finally returned to work in September, 1938. After he had been working for several weeks, the anginal attacks suddenly returned in severe form, and since that time he had been unable to do anything involving exertion or excitement without distress. He stated that his blood pressure had been elevated for at least three years, but that the systolic pressure had never been above 190.

When he entered the hospital, the patient was having a great many attacks of pain each day, and many attacks at night, as well. Nitroglycerine gave prompt relief, and he was taking 40 to 50 tablets of the drug daily. The pain never lasted more than four or five minutes. It was followed by transient weakness of the left hand.

On examination the patient was slightly obese. The heart was borderline in size. The cardiac rhythm was normal, and no significant murmurs were heard. The heart sounds were loud, and there was slight reduplication of the first sound at the apex. The remainder of the physical examination was entirely negative.

The blood pressure was 165/110. Examination of the blood and urine, kidney function tests, and the Kahn test disclosed nothing abnormal. An orthodiagraphic examination of the heart showed questionable, slight enlargement.

A number of electrocardiograms were taken. All of those which were made when the patient was free of pain showed inversion of the T deflection in Leads II and III and slight downward displacement of the RS-T junction in all three limb leads (Fig. 3).

On the morning of Dec. 10, 1938, the patient was told by his physician to stop smoking. He did so, and had no more attacks of pain until Dec. 14, 1938. On this day he was brought to the Heart Station and was asked to smoke a cigarette. A single chest lead (Lead V_5) was taken before he began to smoke and was repeated at intervals thereafter. The control curve showed flat, inverted T waves and very slight downward RS-T displacement. A typical and severe anginal attack began within a few minutes after the patient started to smoke. It was accompanied by downward RS-T displacement of as much as 0.3 millivolt. The electrocardiographic changes began before the pain and outlasted it. Their exact duration was not ascertained. The heart rate rose during the attack from 77 per minute to 115 per minute. The blood pressure was not taken at this time. Another mild attack of pain occurred without obvious cause in the evening of the day of this experiment. On the following day the patient left the hospital. Further information as to the subsequent course of his illness is rather meager.

On Jan. 16, 1939, the patient's home physician wrote that he was still taking about 20 nitroglycerine tablets per day. He was able to walk from seven to fourteen blocks without pain, but had frequent, severe attacks in the early morning hours, some of which had lasted as long as thirty minutes in spite of nitroglycerin at five-minute intervals.

On Jan. 27, 1939, the patient himself stated that he had continued to have attacks, but that these were less frequent and milder than before, and that he had been able to shovel snow without symptoms.

CASE 5.—V. L., an American attorney, aged 50 years, was admitted to the University Hospital on Feb. 11, 1939. He stated that for the preceding 25 years he had frequently experienced a heavy feeling in the epigastrium, accompanied by pyrosis. These symptoms usually developed in the late afternoon, but sometimes came on fifteen to twenty minutes after a meal. They were promptly relieved by soda, which he was taking 3 or 4 times each day. In May, 1938, he began to have very brief attacks of substernal pressure, accompanied by pain high in the back and in both shoulders, with radiation down the outside of the arms as far as the elbows. These attacks were mild, and he paid little attention to them until late in November, 1938, when he had a severe attack in the evening while he was sitting quietly at home. A second attack occurred the same evening, and thereafter he had had attacks daily. In some attacks the pain in the arms was quite severe. Occasionally, there was pain in the left arm only. The distress never lasted more than three or four minutes, and it was never precipitated by exciteement or by exertion. Most of the attacks occurred at night and awakened the patient from sleep. For relief he sat up or got out of bed and walked about his room. Nitroglycerine (1/150 gr.) relieved the discomfort at once. There was no dyspnea during attacks, but there was a transient feeling of weakness after they subsided. The intensity of the substernal distress and the intensity of the pain in the back and arms seemed to vary independently, and one sensation sometimes occurred without the other.

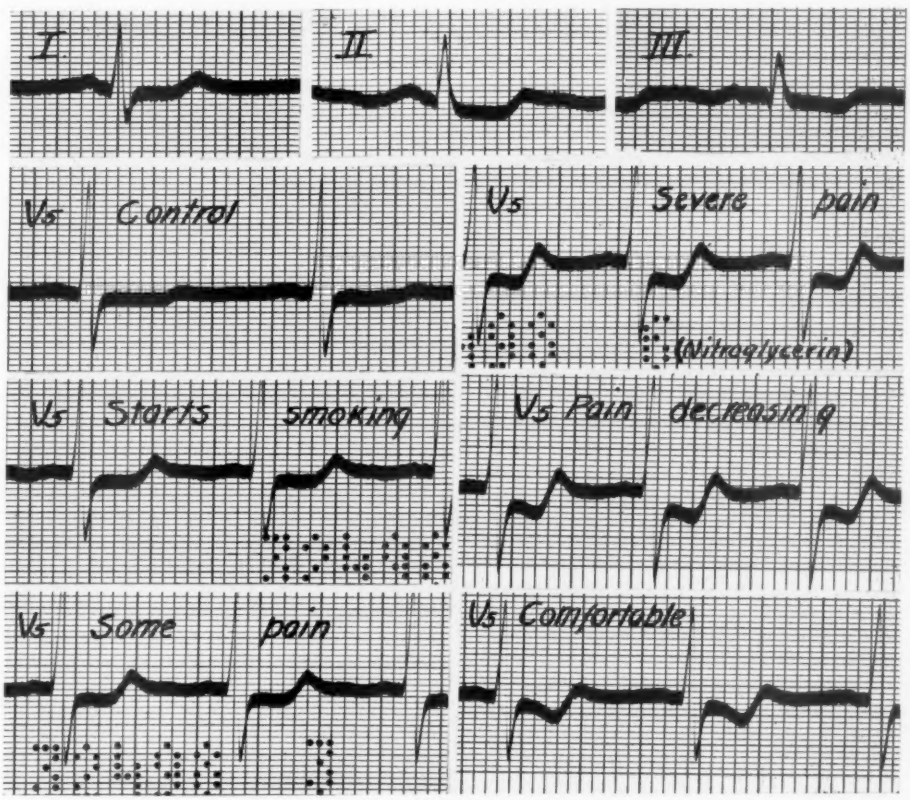

Fig. 3.—Case 4. Top row. Standard electrocardiogram. The remaining curves represent a single precordial lead (V_5), taken before, during, and after an attack of anginal pain induced by smoking and relieved by nitroglycerine.

The past history was negative except for whooping cough, measles, mumps, and chicken pox during childhood, and estivo-autumnal malaria in 1908, and again in

1910. The patient was in the habit of consuming about twenty cigarettes and two or three cups of coffee daily. He used alcohol in moderation.

On physical examination he was moderately obese, but no definite abnormality of any kind was discovered. The blood pressure was 160/100. The Kahn test, gastric analysis, the routine blood cell count, the estimation of the basal metabolic rate, and roentgenologic examination of the cervical spine, the heart and aorta, the gastrointestinal tract, and the gall bladder disclosed no abnormalities. The urine contained a very faint trace of albumin, and a few finely granular casts were found in the sediment. A number of electrocardiograms were taken while the patient was at rest, and one after mild exertion. All of these curves were considered well within normal limits. One of these electrocardiograms, taken on Feb. 11, 1939, is reproduced in Figure 4*A*.

While in the hospital the patient continued to have two or three of his attacks daily. Most of these attacks occurred between 7 P.M. and 8 A.M. Aminophyllin (0.2 Gm. q.i.d.) was given without noticeable effect upon the frequency of the attacks. On one occasion the blood pressure was taken during an attack and was found to be 200/120. There was a daily rise in temperature to 99° or 99.5° F.

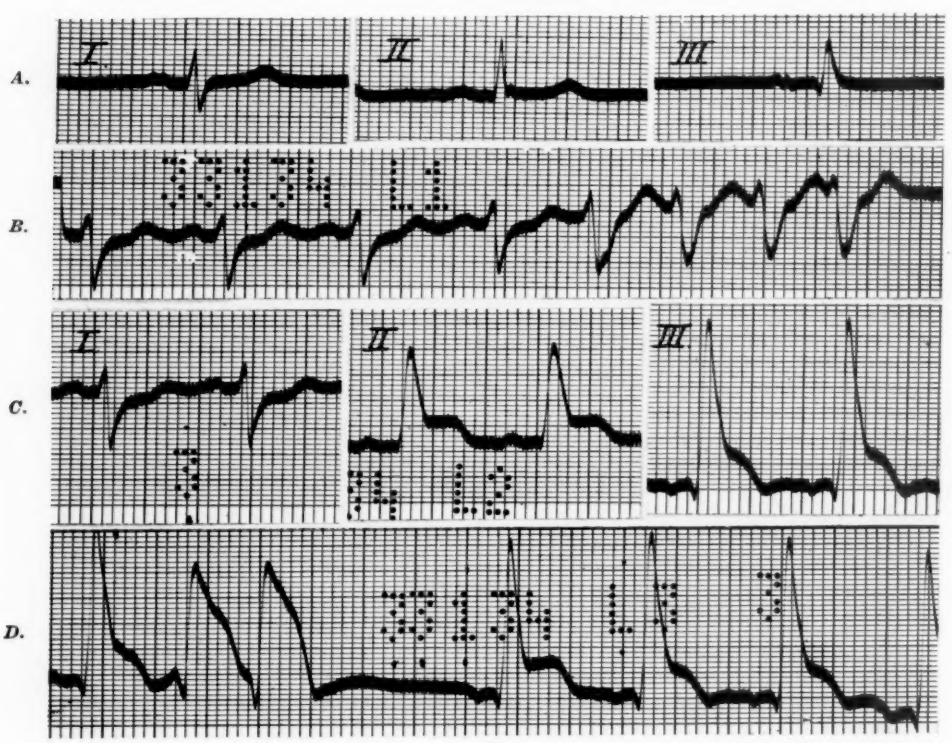

Fig. 4.—Case 5. *A*, Standard electrocardiogram. *B*, Lead I taken during the early stages of a spontaneous attack of anginal pain. *C*, Standard electrocardiogram taken at the height of the attack. *D*, Lead III, showing ventricular extrasystoles of monophasic outline.

On Feb. 18, 1939, a series of electrocardiograms was taken during a severe attack. The earliest curves of this series (Fig. 4*B*) show single ventricular extrasystoles and runs of ventricular extrasystoles constituting very brief paroxysms of ventricular tachycardia. In all of the electrocardiograms which were taken at the height of the distress (Fig. 4*C* and 4*D*), the QRS interval measures approximately 0.16 second, the chief initial deflection (R) is greatly increased in height in Leads II

and III, and the RS-T junction is greatly displaced from the isoelectric level. The RS-T displacement is downward in Lead I and upward in Leads II and III and resembles that seen in the early stages of infarction of the diaphragmatic wall of the heart. The extrasystolic ventricular complexes became practically monophasic as a result of the magnitude of this displacement of the junction of the initial and final deflections.

Following the administration of nitroglycerine the patient's distress disappeared promptly, and within a few minutes the electrocardiogram had practically regained its normal outline.

The patient was discharged from the hospital on Feb. 18, 1939, but was asked to return on Feb. 21, 1939, in order that further electrocardiographic studies might be carried out. A control electrocardiogram taken at 11:42 A.M. on this date shows no abnormalities (Fig. 5*A*). The heart rate at this time was 86 per minute, and the blood pressure was 138/88. The patient was then asked to smoke two cigarettes. When he had finished smoking, at 12:10 P.M., he complained of a slight burning sensation on the lateral aspect of the left upper arm; the heart rate was 94 per minute and the blood pressure was 140/88. The electrocardiogram (Fig. 5*B*) showed slight downward displacement of the RS-T junction in Lead I and pronounced upward displacement of this junction in Leads II and III. At 12:20 P.M. the electrocardiogram had returned to normal; the heart rate was 90 per minute and the blood pressure was exactly the same as at 12:10 P.M.

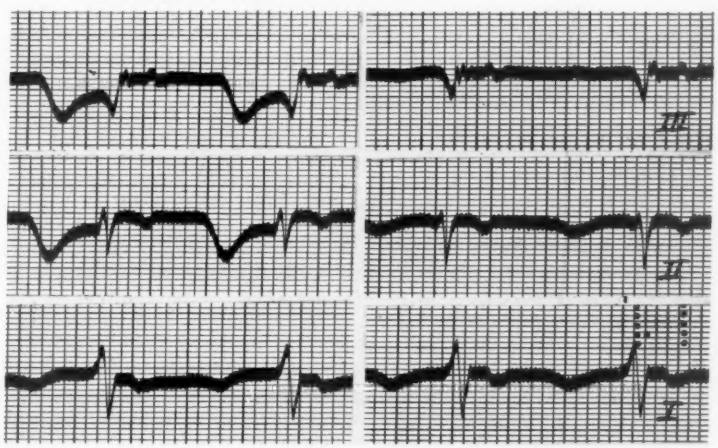

Fig. 5.—Case 5. *A*, Standard electrocardiogram before smoking. *B*, Standard electrocardiogram a few minutes after smoking two cigarettes.

A heavy luncheon had no effect upon the form of the electrocardiogram which was taken at 1:03 P.M., when the heart rate was 100 and the blood pressure 183/80. In the course of the afternoon it was observed that the electrocardiograms which were taken shortly after the patient had finished a cigarette did not always show RS-T displacement. He was then connected to a cathode-ray electrocardiograph so that the electrocardiogram might be observed continuously as a standing wave on the screen of the cathode-ray tube. It was then found that, while he was smoking, pronounced RS-T displacement came and went at frequent intervals. On each occasion it lasted fifteen to twenty seconds only. When he had finished smoking it soon disappeared permanently.

Because of these observations the patient was asked to discontinue smoking. Aminophyllin, erythrol tetranitrate, and quinidine, and a reduction diet were prescribed. He has continued to have attacks, but they have been less frequent and less severe. A study of his sensitivity to foreign proteins is being carried out.

DISCUSSION

The electrocardiographic changes which occurred during a spontaneous attack of anginal pain in Case 3 and those which occurred following exertion sufficiently severe to induce mild pain in Cases 1 and 2 are strikingly similar. In all three instances there was a pronounced increase in the size of the S deflection in Leads II and III and pronounced downward RS-T displacement in Leads II and III. Changes of this kind in the QRS complex have not, so far as we know, been observed in coronary occlusion. The RS-T displacement, however, is similar in magnitude and in kind to that seen immediately following sudden occlusion of the anterior descending branch of the left coronary artery. There is one difference. Following occlusion of the artery mentioned the RS-T displacement is usually definitely discordant, i.e., it is upward in Lead I and downward in Lead III. In the three cases of angina pectoris described, however, the RS-T displacement is either concordant (downward in all three leads) or so inconspicuous in Lead I as to make its classification as concordant or discordant difficult.

Electrocardiographic changes of the same kind, but even greater in magnitude, so far as the RS-T displacement is concerned, were recorded under similar circumstances by Scherf.[1]

The electrocardiographic changes which occurred during a spontaneous attack of anginal pain in Case 5 are of a different kind. Here the RS-T displacement is definitely discordant (downward in Lead I and upward in Leads II and III) and not distinguishable in type or in magnitude from that frequently seen immediately following infarction of the posterior or diaphragmatic wall of the heart. The changes in the QRS complex are striking, but difficult to classify. The great increase in the QRS interval indicates that a pronounced disturbance in intraventricular conduction occurred, but whether this was dependent upon the development of block in the right branch of the His bundle or upon a widespread depression of the specialized ventricular tissues is not clear. It should be noted that prominent Q deflections in Leads II and III, such as are commonly seen following infarction of the posterior wall of the heart, did not appear. Brow and Holman[2] recorded transient RS-T displacement of large magnitude and of this same type during a spontaneous attack of anginal pain. In that instance, however, there was a deepening of the Q deflection in Lead II immediately after the attack, and an electrocardiogram which was taken four months later strongly suggests that there was an infarct in the posterior wall of the heart at that time. As to when this infarction occurred the history gave no unequivocal clue.

The electrocardiographic changes which occurred in Case 4 during an anginal attack induced by smoking were recorded in Lead V_5 only. The

RS-T displacement is similar in magnitude and in kind to that seen in the early stages of infarction of the posterior wall of the heart, but no QRS changes are present.

The electrocardiographic changes described are similar in magnitude and in duration to those produced in animal experiments by temporary occlusion of one of the large coronary arteries. They indicate that the disturbances in the coronary circulation which occur during paroxysms of anginal pain are sometimes of very great magnitude. It is not surprising that sudden death, presumably from ventricular fibrillation, is a not uncommon event in angina pectoris, even when this condition is not complicated by coronary thrombosis.

It seems to be the prevailing opinion that the substernal discomfort and transient electrocardiographic changes which occur in anginal paroxysms are dependent upon myocardial ischemia brought about by an increase in the work of the heart, rather than by a change in the caliber of the coronary arteries affected. When, as in Case 5, pronounced electrocardiographic changes of the kind produced by temporary occlusion of a large coronary artery appear, disappear, and reappear without any material increase in heart rate or in blood pressure, this view is clearly untenable. It must, we think, be admitted that in some instances anginal paroxysms are precipitated by contraction of the coronary arteries involved. Whether contraction of the larger coronary arteries takes place, or whether it is the caliber of the arterioles that changes, it is not possible to say. The character of the electrocardiographic changes suggests that the change in arterial or arteriolar caliber is local, not general. The electrocardiographic changes which are attributed to myocardial ischemia and the subjective changes seem to vary independently both in magnitude and duration. This circumstance, together with the evidence that coronary spasm does sometimes cause anginal paroxysms, makes it seem possible that the stimuli which gave rise to the subjective sensations are of arterial rather than of myocardial origin.

The lack of parallelism between the magnitude of the electrocardiographic changes, and hence we may assume of the disturbances of the coronary circulation, and the work of the heart, as represented by the increase in heart rate, in blood pressure, or in both, was not, in our judgment, confined to Case 5, but also existed in Case 3 and probably in Case 4.

It has been clearly demonstrated that cigarette smoking produces constriction of the peripheral arterioles, both in healthy subjects[3] and in patients with angina pectoris.[4] Healthy young subjects may also display electrocardiographic changes immediately after smoking.[5, 6] Cases have frequently been reported in which precordial pain, not definitely anginal in character, was induced by smoking and disappeared promptly when this habit was given up. A few instances of this kind have come

to the personal attention of the authors. Instances have also been reported in which a patient subject to typical anginal paroxysms could induce an attack by smoking.[4] Cases 4 and 5 apparently belong in this category. It is our opinion that in both of these cases some part of the coronary arterial system was the seat of a disease process, presumably atherosclerotic in nature, and that the affected vessels were abnormally sensitive to nicotine or to some other constituent of cigarette smoke. The observations made in Case 5 strongly support this view. They do not, perhaps, establish it as correct beyond question.

SUMMARY

The pronounced electrocardiographic changes which sometimes occur during a paroxysm of angina pectoris indicate that the disturbance of the coronary circulation which occurs in this condition is at times as great as that produced by the sudden occlusion of a large coronary artery.

Attacks of anginal pain may occur which are accompanied by profound alterations of the electrocardiogram under circumstances which make it necessary to assume that the attendant myocardial ischemia is due to a change in the caliber of the coronary arteries affected, rather than to an increase in the work of the heart alone.

Nicotine or some other constituent of cigarette smoke sometimes induces coronary "spasm" in patients who are subject to angina pectoris.

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LUMBAR SYMPATHECTOMY IN THE TREATMENT OF SELECTED CASES OF PERIPHERAL ARTERIOSCLEROTIC DISEASE

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IT IS generally agreed that a therapeutic increase in the volume of blood flow through ischemic tissue is dependent on methods which are capable of producing a dilatation of the small vessel bed in the ischemic part. It has also been established that a collateral arterial network will hypertrophy in response to an increase in the volume of flow through it; and that, for practical therapeutic purposes, such an increase is also dependent on a diminution in the peripheral resistance to blood flow, as brought about by dilatation of the small vessel bed into which that collateral network ultimately empties. If sympathetic vasoconstrictor impulses should inhibit the therapeutic relaxation of the arteriolar bed, or render such relaxation ephemeral, then conservative vasodilating therapy will neither relieve the ischemic condition nor increase the potential vascular reserve through hypertrophy of a collateral arterial network. It has been observed that sympathetic vasoconstrictor tone constitutes such a barrier to medical treatment in a significant number of instances of arteriosclerotic disease of the lower extremity. The following is a case in point. It illustrates what may be the eventual outcome when sympathetic vasoconstrictor tone is not removed surgically.

CASE 60141.—M. D., a 61-year-old white man, was first seen on Aug. 21, 1937. During the previous year he had suffered from intermittent claudication, with pain and severe subjective coldness of his right foot. Examination showed that there was no palpable pulsation in the right dorsalis pedis or posterior tibial artery. Oscillometry revealed a trace of pulsation at the level of the lower leg. There was some pallor of the right foot on elevation, but no rubor or cyanosis, and the nutritional status was good. The foot was cold to the touch, but, following a procaine block of the right lumbar sympathetic trunk, it became palpably warm, and the skin temperatures of the toes rose from 24.5° C. to a vasodilatation level of 29.5° C. (Fig. 1). The patient was given a course of conservative treatments consisting of intravenous injections of hypertonic saline, short-wave diathermy, and treatment with the intermittent venous occlusion cuff twice a week. At home he took daily, warm, leg baths, Buerger's exercises, and whiskey. He was given detailed instructions on the care of his feet. Three months of this treatment gave no relief. A Landis test was then done to ascertain whether conservative vasodilating treatment was actually capable of relaxing the small vessel bed in the foot. The patient's arms were immersed in water at 120° F., and his body was wrapped in blankets. At the end of forty minutes the test had to be discontinued because it was too enervating. No rise occurred in the skin temperatures of the toes in this forty-minute period (Fig. 2).

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Therefore, it was felt that conservative vasodilating therapy could not possibly be effective in the face of such persistent sympathetic vasoconstrictor tone, and a lumbar sympathectomy was advised. However, the patient had a dread of any operative interference, and he refused. This patient was followed for a period of almost three years, and during this time he received intensive, conservative, vasodilating therapy; but his condition, both subjectively and objectively, grew slowly worse. Two years from the time he was first seen, advanced color changes, with atrophy of the skin and subcutaneous tissue of the foot, appeared. The pain was very severe. The condition progressed to massive gangrene of the foot, and, in June, 1940, the foot was amputated.

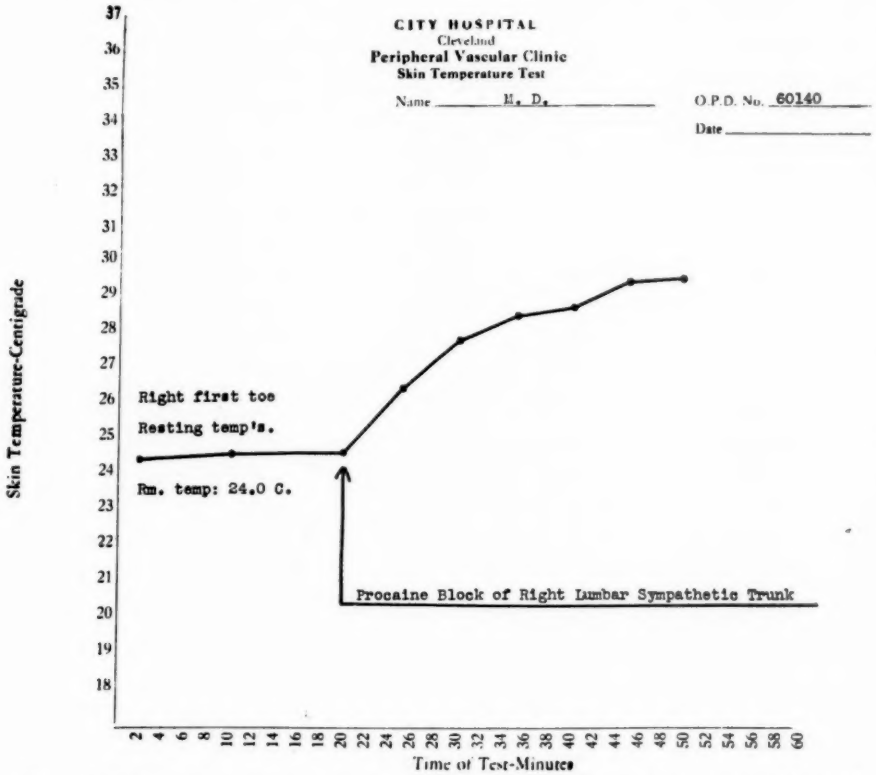

Fig. 1.—Figure shows rise in skin temperature of right foot after procaine block of lumbar sympathetic trunk.

At the present writing, twenty lumbar sympathectomies have been performed in cases of this kind. Of these patients, twelve have been observed for a period of a year or longer. The results obtained are summarized in Table I. (A year of observation is considered the minimum for drawing valid conclusions concerning the benefit derived from any form of treatment in peripheral arteriosclerotic disease.) Following operation, these patients received no further therapy except that associated with the routine care of the feet or the local treatment of ulceration. Clinically, these cases have been characterized preoperatively by an absence of marked pallor of the foot on elevation or rubor on dependency,

by soft, pliable skin and subcutaneous tissue, usually, but not always, by some degree of pulsation in the lower leg, as measured with the oscillometer, by a venous filling time of not more than fifteen seconds, by severe subjective and objective coldness of the foot, and by a rapid rise in the skin temperatures of all the toes to a vasodilatation level of at least 28° C. after procaine block of the sympathetic nervous pathways to the blood vessels of the foot, and by the failure of conservative treatment to ameliorate symptoms or to heal ulceration. In short, they were cases in which the collateral vascular network was not incapable of hypertrophy, and in which the small vessel bed had retained its flexibility. The following detailed reports illustrate what can be expected in this type of case in the way of relief of symptoms, healing of ulcerations, and increase in the vascular reserve through hypertrophy of a collateral circulation when vasoconstrictor tone is removed surgically.

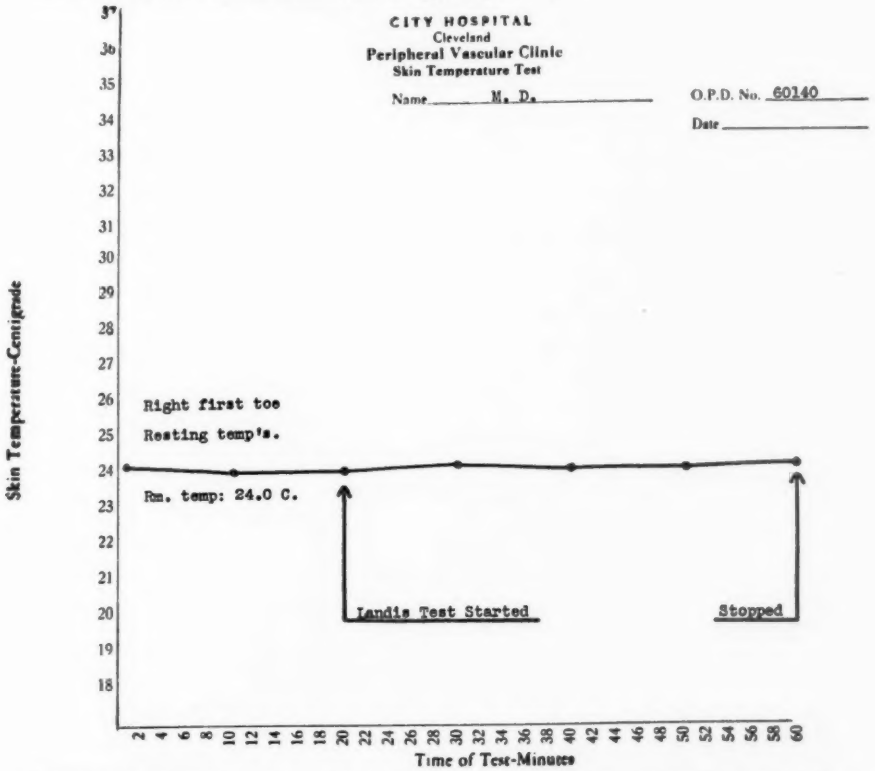

Fig. 2.—Illustration shows failure of powerful vasodilating measure, the Landis test, to duplicate the rise in skin temperature obtained with procaine block of sympathetic vasoconstrictor impulses to blood vessels of foot.

The first has to do with the relief of severe, persistent coldness, numbness, and paresthesias. After lumbar sympathectomy the disappearance of such symptoms is immediate. Not uncommonly, on the day after the operation, the patient remarks that for the first time in years the sympathectomized foot feels "alive."

TABLE I

SUMMARY OF CASES OF PERIPHERAL ARTERIOSCLEROTIC DISEASE IN WHICH LUMBAR SYMPATHECTOMY WAS DONE AND THE PATIENT OBSERVED FOR PERIOD OF TWELVE MONTHS OR LONGER

	PREOPERATIVE OBSERVATIONS							POSTOPERATIVE STATUS					
NO.	EXTREMITY	AGE (YR.)	DORS. PED.	POST. TIB.	SKIN TEMP.*	OSCILLOMETRIC RDGS.†	SYMPTOMS	INTERVAL (MO.)	DORS. PED.	POST. TIB.	SKIN TEMP.	OSCILLOMETRIC RDGS.	SYMPTOMS
1	P. B.	56	Absent	Absent	22.0	0.2	Severe int. cl.; cold, numb foot	12	Absent	Absent	33.0	1.0	Slight fatigue at end of full day's work
2	P. B.	56	Absent	Absent	22.0	0.5	Severe int. cl.; cold, numb foot	12	Absent	Absent	33.5	2.5	None
3	O. C.	68	Absent	Absent	23.0	1.0	Painful ulcers on fourth and fifth toes	12	Absent	Absent	32.5	2.5	None; ulcers healed
4	I. M.	56	Absent	Absent	25.0	0.2	Severe int. cl.; cold, numb foot	12	Absent	Absent	32.5	2.3	Slight fatigue only with rapid walking
5	E. G.	57	Weak	Absent	22.0	1.5	Severe int. cl.; cold, numb foot	14	Weak	Absent	33.0	3.0	None
6	E. G.	57	Absent	Absent	22.0	1.0	Severe int. cl.; cold, numb foot	14	Absent	Absent	32.0	2.0	Slight fatigue at end of full day's work
7	J. G.	60	Absent	Absent	22.5	0.0	Severe int. cl.; cold, numb foot	17	Absent	Absent	32.0	1.5	None
8	O. H.	55	Absent	Absent	24.0	0.0	Severe int. cl.; cold, numb foot	17	Absent	Absent	30.5	0.5	Intermittent claudication not improved
9	A. F.	61	Absent	Absent	23.0	0.5	Severe int. cl.; cold, numb foot	18	Absent	Absent	32.0	1.5	Slight fatigue after walking long distance
10	S. B.	58	Absent	Absent	22.0	0.1	Painful ulcer in nail bed of first toe; cold foot; severe int. cl.	20	Absent	Absent	30.0	0.5	None in foot; ulcer healed; intermittent claudication not improved
11	K. S.	57	Weak	Weak	22.5	1.5	Painful, cold, numb foot	21	Weak	Weak	32.5	2.5	None
12	K. S.	57	Absent	Absent	22.5	1.0	Painful, cold, numb foot	25	Absent	Absent	32.0	2.0	None

*Skin temperatures from pad first toe at room temperatures (22.0° to 24.0° C.).
†Oscillometric readings taken at supramalleolar level.

CASE 80371.—K. S., a white, female diabetic, aged 57, came under observation May 6, 1938. For three years, even in warm weather, she had suffered from severe coldness, numbness, and paresthesias of the feet. During this period she took daily warm foot baths and vasodilating drugs without relief. Lately, the symptoms had become more severe, a burning type of pain had appeared in her feet, and she was threatened with incapacitation. Examination showed that the pulsation in the right dorsalis pedis and posterior tibial arteries was barely palpable, and no pulsation was felt in the left dorsalis pedis and posterior tibial arteries. Oscillometric examination revealed a diminution of pulsation in the region of the lower legs. Roentgenograms showed calcification in the long arteries of the legs. There were no marked color changes, and the nutritional status of the feet was good. At a room temperature of 24° C., both feet were cold to the touch, but, after procaine block of both lumbar sympathetic trunks, they warmed rapidly; the skin temperatures of the toes reached vasodilatation levels ranging from 30° C. to 32° C. The procaine blocks gave considerable subjective relief for a few hours, and therefore an alcohol block of the left lumbar sympathetic trunk was done. This gave complete relief of symptoms for three weeks. However, at the end of that time the beneficial effects of the block waned, and all of the symptoms returned. The block was not repeated because the first one resulted in an alcoholic neuritis of the lateral cutaneous nerve of the thigh (this will be again referred to later in the paper). A left-sided lumbar sympathectomy was performed in June, 1938. The operation gave immediate and complete relief of all symptoms in the left foot. She returned voluntarily to the Clinic in October, 1938, asking that the right foot also be sympathectomized. When last seen, in July, 1940, she stated that her feet had been symptom free since the operation. The skin temperatures of the toes ranged between 30° C. and 32° C. A faint pulsation was still palpable in the right dorsalis pedis and posterior tibial arteries. The oscillometric readings in both legs had almost doubled their preoperative magnitude.

In some cases of painful ulceration of the affected limb, sympathectomy may expedite the healing of the ulceration and gradually relieve the pain. The following cases illustrate the relief of pain associated with ulceration.

O. C., a 68-year-old white woman, was first seen on July 21, 1939. For nine months she had been suffering from increasingly severe pain, subjective coldness, numbness, and paresthesias of the left foot. More recently, ulcers had appeared on the fourth and fifth toes of the left foot. Examination showed that no pulsation was palpable in the left dorsalis pedis or posterior tibial artery. Oscillometric study revealed diminished pulsation in the region of the lower leg. No marked color changes were present except for some cyanosis of the fourth and fifth toes, which were superficially ulcerated. There was no atrophy of the skin or subcutaneous tissue. At a room temperature of 24° C., the foot was very cold to the touch, but, after procaine block of the posterior tibial nerve, the foot became palpably warm, and the skin temperatures of the toes rose to vasodilatation levels ranging from 29° C. to 30° C. During the following three months she received intravenous injections of calcium gluconate and short-wave diathermy to the left foot twice a week, and daily, warm, leg baths, followed by treatment with the intermittent venous occlusion cuff at home. This treatment gave no relief from the symptoms, which became increasingly severe, and the ulceration of the toes progressed. Despite her age, she appeared to be a good operative risk, and a left-sided lumbar sympathectomy was performed in October, 1939. During the two months immediately following the operation there was a gradual decrease in the severity of symptoms, accompanied by healing of the ulcerations. Six months after the operation she was symptom

free, and the ulcerations had completely healed. The foot was warm and dry, had a good color, and appeared normal in every way. In October, 1940, twelve months after sympathectomy, the improvement had been maintained. The skin temperatures of the toes ranged from 31.0° C. to 32.5° C.

S. B., a 58-year-old white man, was seen Feb. 21, 1939. For a year he had suffered continuous, excruciating pain in his right great toe, and persistent, severe, subjective coldness and numbness of the right foot. The painful toe was ulcerated. During this year he had received intravenous injections of hypertonic saline with no relief. Examination showed that no pulsation was palpable in the right dorsalis pedis or posterior tibial artery. Oscillometric study revealed a slight trace of pulsation in the region of the lower leg. There were no marked color changes except for some cyanosis of the right great toe, which was ulcerated along the margins of the nail. There was no atrophy of the skin or subcutaneous tissue. At a room temperature of 24° C., the foot was cold to the touch and covered with perspiration. After procaine block of the posterior tibial nerve, the foot became palpably warm, and the skin temperatures of the toes rose to vasodilatation levels ranging from 29° C. to 30° C. During the following two months he received additional conservative therapy consisting of warm leg baths twice a day, whiskey, and treatment with the intermittent venous occlusion cuff. He also received intravenous injections of 5 per cent saline twice a week. No relief of symptoms was obtained, and, in April, 1939, a right-sided lumbar sympathectomy was performed. During the following two months complete healing of the ulceration, with relief of symptoms, took place. In October, 1940, the skin temperatures of all the toes ranged between 31° C. and 31.5° C. The nutritional status of the right foot appeared to be good.

There is some difference of opinion regarding the beneficial effects of sympathectomy in cases of ischemic muscular pain, the so-called intermittent claudication. I do not believe that lumbar sympathectomy is ever indicated in the treatment of intermittent claudication per se, because such pain does not, in itself, indicate an ischemic condition the nature of which jeopardizes the structural integrity of the limb. However, the question arises as to what effect lumbar sympathectomy has on ischemic muscular pain when it is present in the kind of case under discussion. There is some experimental evidence[1-4] which appears to indicate that the circulation through peripheral muscle tissue is not influenced by sympathetic vasoconstrictor impulses, and that, therefore, lumbar sympathectomy should have no effect on intermittent claudication. However, Grimson and Shen[5] tested the vasomotor responses of skinned legs, and report directly opposite conclusions. In the group of cases summarized in Table I, intermittent claudication disappeared or became markedly diminished in seven out of nine instances following lumbar sympathectomy (see Table I). The presence of a few, very small, sclerotic muscle vessels without distal anastomotic connections, with an available collateral circulation, could have been responsible for the two failures. Only a small quantity of muscle tissue need be ischemic to give rise to considerable pain. As Kellgren[6] has recently shown, a very minute quantity of an irritating substance, e.g., 5 minims of 6 per cent saline, when injected directly into muscle tissue, produces

intense pain which is felt not only at the site of injection, but over widespread adjacent cutaneous areas as well.

The relief of intermittent claudication, when it was obtained, followed a definite pattern. An immediate increase in walking capacity was rarely observed. However, the cramp-like pain was often replaced at once by a feeling of severe fatigue. As a collateral circulation developed, walking capacity gradually increased. At times, it took a year for the maximum benefit to be obtained. The following two cases not only illustrate relief of intermittent claudication, but also present demonstrable oscillometric evidence of the growth of a collateral circulation following lumbar sympathectomy.

CASE 40982.—J. G., a 60-year-old white man, was admitted to the Peripheral Vascular Clinic at the Cleveland City Hospital on Jan. 27, 1939. During the previous year he had suffered severe aching pain, subjective coldness, and numbness of the left foot. Intermittent claudication was also present, involving the left calf and foot. He could walk only two blocks before the onset of muscular cramps forced him to stop and rest. Examination showed no marked color changes or atrophy of the skin or subcutaneous tissue of the left foot. No pulsation was palpable in the left dorsalis pedis or posterior tibial artery. Oscillometric readings at the level of the lower leg were zero. At a room temperature of 24° C., the foot was very cold, but, after procaine block of the left lumbar sympathetic trunk, the foot warmed rapidly, and the skin temperatures of all the toes rose to vasodilatation levels ranging from 30° C. to 31° C. A left-sided lumbar sympathectomy was performed in February, 1939. One month after sympathectomy the foot symptoms were completely relieved. However, his walking capacity had not increased, although he now experienced severe fatigue instead of the cramp-like pain he had felt prior to the operation. Oscillometric readings at the level of the lower leg were still zero. Three months later he was able to walk a much longer distance before the onset of fatigue. At this time the oscillometer registered a trace of pulsation in the region of the lower leg. He was seen at regular intervals during the following year, and, in July, 1940, seventeen months after the operation, all his symptoms, including the intermittent claudication, had disappeared. The nutritional status and color of the foot were excellent. The skin temperatures of the toes ranged from 32° C. to 33° C. There was still no palpable pulsation in the dorsalis pedis and posterior tibial arteries. However, the oscillometer now revealed an excellent pulsation in the same segment of the leg where none was present prior to the sympathectomy. This marked increase in pulsation, which developed gradually during the seventeen months following sympathectomy, is illustrated in the oscillometric tracings shown in Fig. 3. Since there is no reason to believe that sympathectomy restores elasticity to arteries which are already diseased, such an increase in magnitude can only be interpreted as the result of hypertrophy of healthy collateral arteries.

I. M., a 56-year-old white man, was seen Aug. 12, 1938. For several months he had suffered from subjective coldness of the right foot, and from aching, cramp-like pains in the muscles of his right calf which appeared on walking. He could walk only a few blocks before the onset of pain forced him to rest. Examination showed that there were no color changes or atrophy of the skin or subcutaneous tissue of the right foot. No pulsation could be felt in the right dorsalis pedis and posterior tibial arteries. A roentgenogram showed calcification of the dorsalis pedis artery. The oscillometer revealed only a trace of pulsation in the region of the right lower leg. At a room temperature of 24° C., the foot was cold to the touch, but, after procaine block of the posterior tibial nerve, the foot warmed rapidly, and the skin

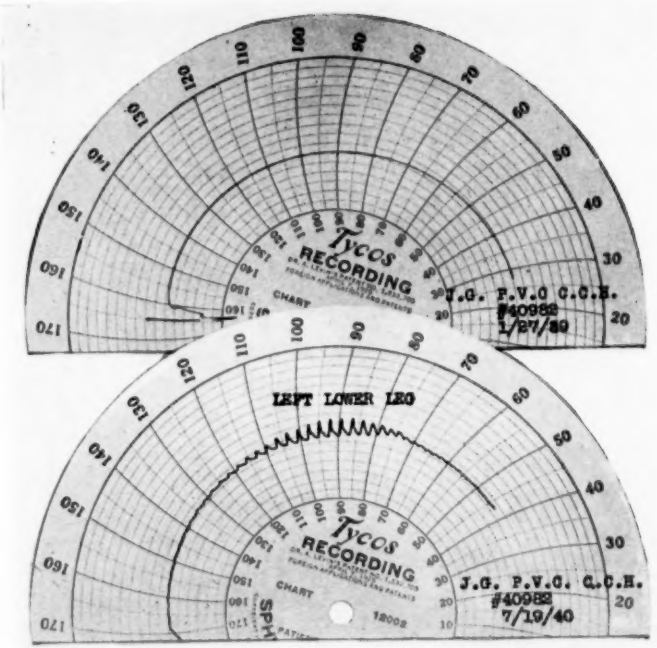

Fig. 3.—Illustration shows increase in magnitude of pulsation in region of lower leg which occurred gradually during a period of seventeen months following lumbar sympathectomy. Such an increase can be interpreted only as the result of hypertrophy of a collateral circulation. Upper tracing was taken before left lumbar sympathectomy; lower tracing was taken seventeen months after sympathectomy.

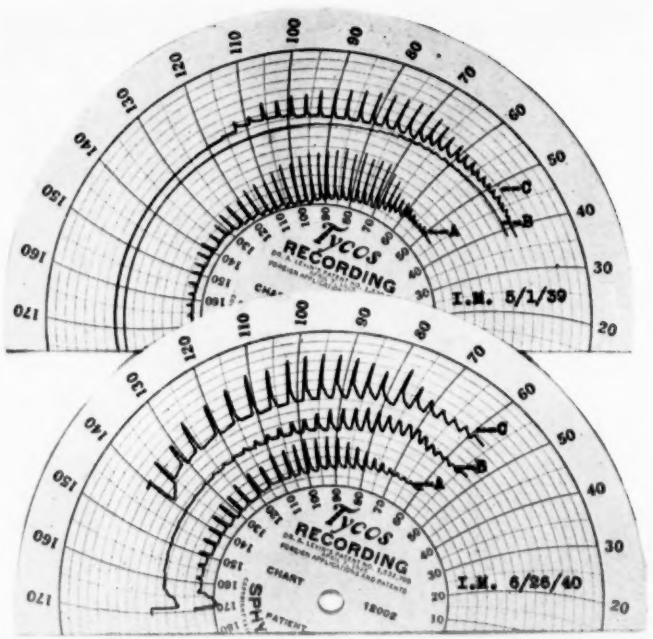

Fig. 4.—Illustration shows marked increase in magnitude of pulsation in region of right lower leg during the twelve-month period following lumbar sympathectomy. Note decrease in magnitude of arterial pulsation in opposite lower leg during this same period to a point where it was less than that in the lower forearm. This indicates beginning arteriosclerotic disease in the left lower extremity.[9, 10] *A*, Left lower leg; *B*, right lower leg; *C*, right lower forearm. Upper tracing was taken before right lumbar sympathectomy; lower tracing was taken twelve months after sympathectomy.

temperatures of the toes reached vasodilatation levels ranging from 32° C. to 33° C. During the following eight months he received intensive conservative vasodilating therapy without relief. This treatment included whiskey and daily, warm, leg baths, followed by treatment with the intermittent venous occlusion cuff, short-wave diathermy, intravenous injections of hypertonic saline, and the administration of

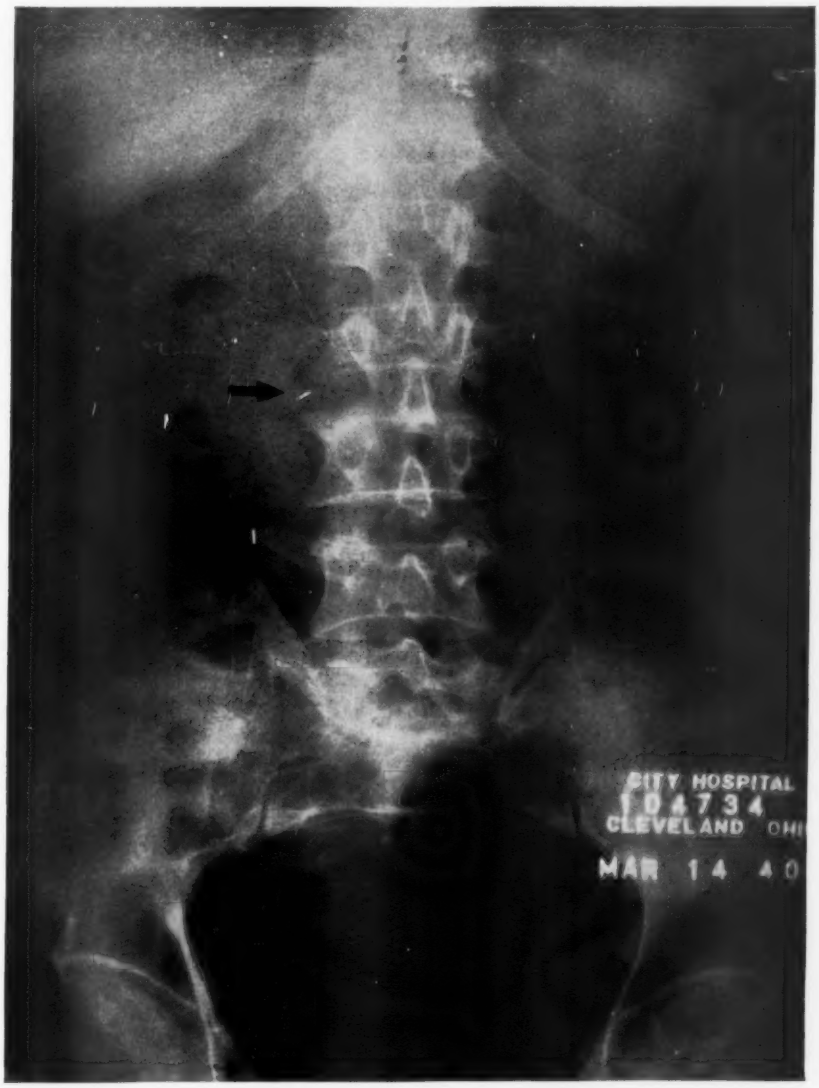

Fig. 5.—Arrows indicate shadows of silver clips on severed ends of lumbar sympathetic trunk. Note that trunk has been severed at upper pole of third lumbar vertebra, and that the caudal portion has been buried in adjacent psoas muscle. This procedure denervates the cutaneous vessels of the foot and lower two-thirds of the leg, and the popliteal artery and its deep branches.

deproteinated pancreatic extract. In May, 1939, a right-sided lumbar sympathectomy was performed. He was seen one month after operation. At this time the foot symptoms had disappeared, but his walking capacity had not increased. However,

he now experienced severe fatigue instead of cramps. Oscillometric examination at this time showed no increase in the magnitude of pulsation in the region of the lower leg. He was not seen again until July, 1940, fourteen months after the sympathectomy. At this time, walking at a moderate rate of speed caused no fatigue. The color and nutritional status of the foot were normal. The skin temperatures of the toes ranged from 31.5° C. to 32.5° C. No pulsation could be felt in the dorsalis pedis or posterior tibial arteries. However, the oscillometric reading now revealed a definite pulsation in the same segment of the leg where only a trace had been present prior to the sympathectomy (Fig. 4).

Table I lists the oscillometric readings which were taken at the level of the lower leg immediately preceding sympathectomy, and after a postoperative interval of twelve to twenty-five months. It will be noted that some degree of increase in the magnitude of the pulsation occurred in every instance. For reasons stated, this is construed as valid evidence of the hypertrophy of a collateral arterial network. In none of these cases was an increase in the magnitude of pulsation observed immediately after sympathectomy. This rules out the possibility that these increases in the magnitude of pulsation were the result of a simple diminution in the tonus of the vessels, rather than an actual hypertrophy of collateral arteries.

The surgical technique used to denervate these extremities has been described elsewhere.[7] It is a simplified form of lumbar sympathectomy. Briefly, the technique is as follows. Through a muscle-splitting extraperitoneal approach, as described by Pearl,[8] the lumbar sympathetic trunk is exposed on the upper pole of the third lumbar vertebra at the inner margin of the psoas major muscle. The trunk is divided at this point, and the distal, cut end is stripped from the body of the third lumbar vertebra and buried in the adjacent psoas muscle (Fig. 5). The operation is easily and quickly performed, and causes no more shock than an appendectomy or simple herniorrhaphy. The blood vessels which are denervated by this procedure are the popliteal artery and its deep branches, and the cutaneous vessels of the foot and lower two-thirds of the leg.

I have discontinued the use of paravertebral alcohol block of the lumbar sympathetic ganglia. Too often, an alcoholic neuritis of the lateral cutaneous nerve of the thigh has occurred. The resultant pain has been as disabling as that for the relief of which the block was done.

I should like to express my appreciation to Dr. Roy W. Scott for his advice and criticism, and to his associates for their cooperation in deciding whether or not these patients were operable.

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THE EFFECT OF DIFFUSE PERICARDITIS ON THE ELECTROCARDIOGRAPHIC PATTERN OF RECENT MYOCARDIAL INFARCTION

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THE criteria for the electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction were formulated by Barnes,[1] who pointed out that the reciprocal relationship between Leads I and III which is found in classical cases of uncomplicated recent myocardial infarction is absent. When pericarditis occurs in cases of recent myocardial infarction, he states, elevation of S-T in one of these leads with depression in the other, or an upright coronary T in one of these leads with an inverted one in the other, is usually not found. Instead, the S-T segment is elevated in all the limb leads, and, later, T may become inverted in all limb leads. Recently the subject was reviewed by Winternitz and Langendorf,[2] who collected from the literature twenty-two cases of recent myocardial infarction with an electrocardiographic pattern similar to that reported by Barnes; in these cases a pericardial friction rub had been observed clinically or pericarditis had been found at necropsy, and to these they added three autopsy cases of their own. It would appear that the special modifications of the electrocardiographic pattern when there is a complicating pericarditis are limited to the generalized form. Localized pericarditis limited to a small area over the infarct does not seem to cause modifications of the S-T-T pattern which would be anticipated from the infarct itself. This is in accord with the effect on the electrocardiogram of experimental ligation of the coronary arteries of the dog and of localized pericarditis (Barnes and Mann,[3] Burchell, Barnes, and Mann[4]). Diffuse pericarditis complicating myocardial infarction is not an uncommon occurrence. Thus, Stewart and Turner[5] found ten cases (16.6 per cent) of generalized pericarditis in sixty autopsy cases of myocardial infarction; Saphir, Priest, Hamburger, and Katz[6] observed four out of thirty-four cases (11.7 per cent); Bohning and Katz[7] noted three out of twenty-seven cases (11.1 per cent); Jervell[8] recorded five out of twenty-six cases (19.2 per cent); and Büchner, Weber, and Haager[9] found two out of nine autopsy cases (22.2 per cent). Thus, out of 156 autopsy cases of recent myocardial infarction which have been reported, there was a complicating, diffuse pericarditis in twenty-four (15.3 per cent).

However, there is a lack of sufficient data in the literature on the changes in the electrocardiogram of recent myocardial infarction which

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are produced by complicating, diffuse pericarditis. It might be anticipated that, when diffuse pericarditis complicates recent myocardial infarction, the electrocardiogram would take on some of the changes which occur in diffuse pericarditis without infarction, as described by Winternitz and Langendorf,[2] among others, or at least that it would show a composite of the contour seen in the two conditions. In this paper we wish to report observations upon two additional autopsy cases, and to discuss the significance of similar changes in cases in which the diagnosis was not proved by autopsy. The latter is important because it is known that the classical electrocardiographic pattern of infarction, with discordancy of the S-T-T segments in Leads I and III, does not always

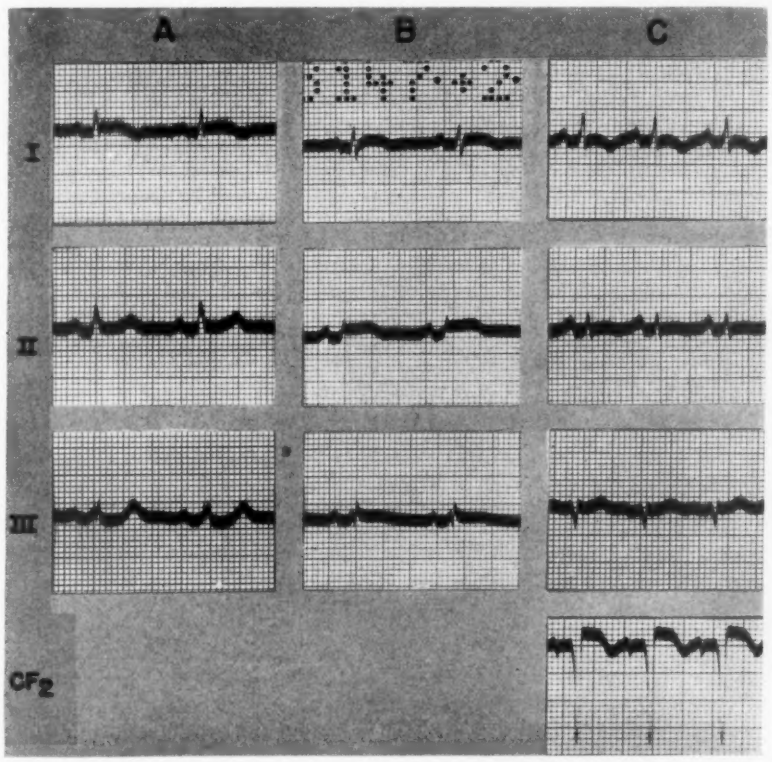

Fig. 1.—(Case 1.) The patient had four severe attacks of angina pectoris between April 20, 1933 and May 4, 1933. Record *A* was taken on May 4, 1933, *B* on May 8, 1933, *C* on May 31, 1933. Autopsy, June 2, 1933, revealed recent infarction of the apical portion of the left ventricle and diffuse fibrinous pericarditis, with obliteration of the entire pericardial sac. Records *A* and *C* show changes of the anterior wall type; *A* shows discordant S-T changes in Leads I and III, *C* shows discordant T changes in Leads I and III. Record *B* shows a transient concordant elevation of the S-T segment in all limb leads.

occur. This has been emphasized in publications from this department (Bohning and Katz,[7] Weinberg and Katz[10]). A number of reasons have been advanced by Weinberg and Katz[10] to account for the variations from the classical pattern of recent myocardial infarction, and these deviations in pattern may, in the absence of diffuse pericarditis, bear some resemblance to the curves to be expected with this complication.

METHOD OF STUDY

In order to see whether the criteria for the electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction could be made more precisely, the electrocardiograms in 380 consecutive cases of what was diagnosed as recent myocardial infarction were examined. From these, thirty-nine cases were selected, including the two with autopsies already referred to, in which there were changes suggesting the possibility of a complicating diffuse pericarditis, and in which these changes could not be attributed to preponderant ventricular hypertrophy or intraventricular block.

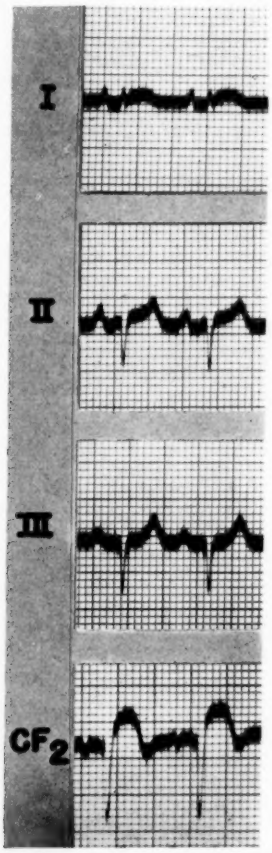

Fig. 2.—(Case 2.) The patient had the attack on May 18, 1935, and a pericardial friction rub was heard on May 23, 1935. The record was taken on May 23, 1935. Autopsy, June 10, 1935, revealed an organizing infarct of the septum and of the anterior wall and of the apex of the left ventricle, with organizing, diffuse, adhesive pericarditis. The electrocardiogram shows an anterior wall infarction pattern in the S-T stage, with no discordant S-T changes in Leads I and III.

The criteria which were used fell into one or more of the following three groups:

1. Concordant elevation of S-T in the limb leads.

2. Concordant inversion of a coronary type of T wave in the limb leads.

3. Absence of a discordant deviation of S-T in Leads I and III, with a marked S-T elevation in one of these leads, i.e., $S\text{-}T_1$ isoelectric and $S\text{-}T_3$ markedly elevated, or vice versa.

A summary of the protocols of these thirty-nine cases is shown in Table I. The cases were next subdivided into four groups, according to the type of the S-T-T pattern in the limb leads and the QRS pattern in these and in chest leads CF_2 and CF_4, as well. The subdivisions were:

1. Anterior wall type of myocardial infarction.
2. Posterior wall type of myocardial infarction.
3. Combined anterior and posterior wall types.
4. Atypical types.

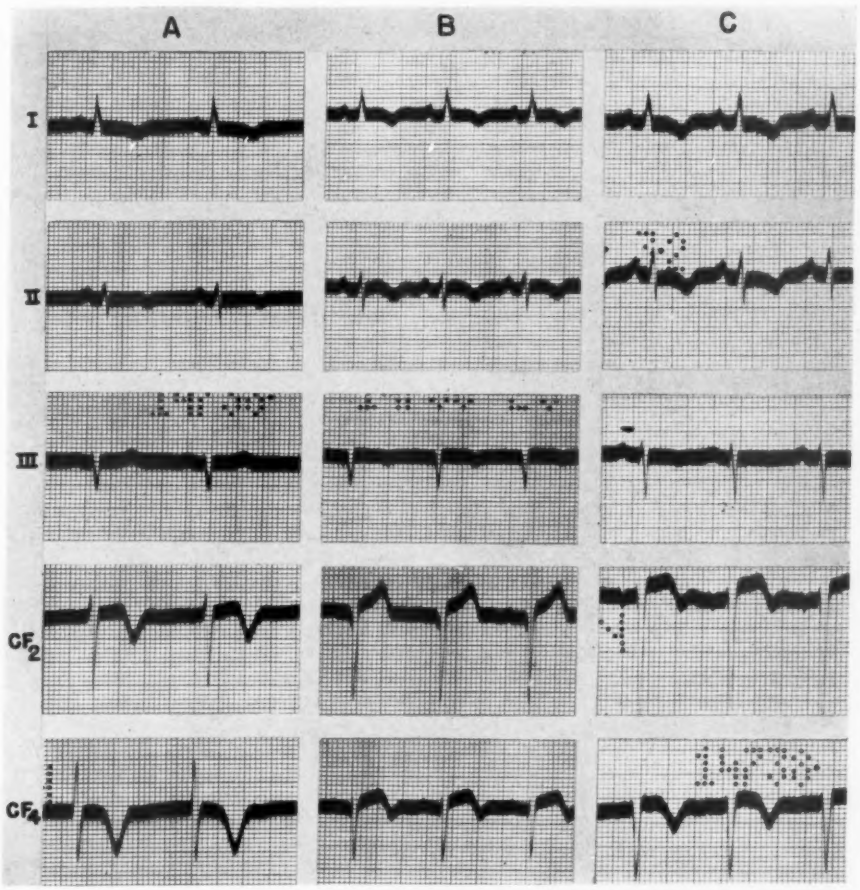

Fig. 3.—(Case 9.) The patient had an attack on June 12, 1939, and a pericardial friction rub was heard on June 20, 1939. Record *A* was taken on June 16, 1939, *B* on June 28, 1939, *C* on August 1, 1939. The electrocardiograms show changes of the anterior wall type. However, the T wave became inverted in all limb leads. For discussion, see text.

Each was further divided into the S-T and T stages. The criteria used for each, the number of cases in each group, the number of autopsies, and the figure illustrating a typical example are assembled in Table II.

TABLE I

CASE	CLASSIFICATION SEE TABLE II	ILLUS. IN FIG.	SEX	AGE	PERICARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTROCARDIOGRAMS	S-T STAGE	T STAGE	EVOLUTION OF "T_N"	S-T AND T IN CHEST LEADS
1	1A	1	M	49	-	6/2/33 Infarction of the apex of the left ventricle, with diffuse pericarditis.	4/20/33 5/ 4/33	5/ 4/33 5/ 8/33 5/16/33 5/31/33	concordant	discordant	-	CF_2 anterior wall type
2	1A	2	M	42	5/23/35	6/10/35 Infarction of the septum, anterior wall, and apex of the left ventricle, with diffuse adhesive pericarditis.	5/18/35	5/23/35	absence of discordance	-	-	CF_2 anterior wall type
3	1A	-	M	53	-	-	4/26/39	5/ 1/39 5/ 3/39	concordant	-	-	CF_2, CF_4 anterior wall type
4	1A	-	M	67	-	-	10/ 5/37	10/ 8/37 10/18/37	concordant	discordant	-	CF_2 anterior wall type
5	1A	-	M	49	2/25/36	-	2/23/36	2/28/36 3/ 2/36 3/31/37	concordant	discordant	-	CF_2 anterior wall type
6	1A & B	-	M	37	6/10/31	-	6/ 1/31	6/ 8/31 6/18/31 7/ 1/31 7/10/31 7/18/31	concordant	concordant	4 weeks	-
7	1A	-	M	65	-	-	10/11/36	10/16/36 10/19/36	concordant	-	-	CF_2 anterior wall type; S-T elevation more marked when S-T elevated in all limb leads

8	1A & B	-	F	55	4/ 1/31	-	3/31/32	1/ 7/31 4/ 1/32 4/ 5/32 4/18/32 4/26/32 5/ 2/32	concord-ant	concord-ant	2 days, S-T still elevated	
9	1B	3	M	65	6/20/39	-	6/12/39	6/16/39 6/28/39 8/ 1/39	-	concord-ant	16 days	CF_2, CF_4 anterior wall type
10	1B	-	M	66	-	-	2/20/37 ?	3/10/37 3/23/37	-	concord-ant	5 weeks	CF_2 anterior wall type
11	1B	-	M	59	-	-	11/29/36	12/ 2/36 12/ 5/36 12/11/36 12/18/36 12/23/36 12/30/36 1/22/37	discord-ant	concord-ant	13 days	CF_2 S-T elevated, T upright and pointed
12	1B	-	F	50	-	-	?	2/ 9/39 3/24/39 7/27/39	-	concord-ant	?	CF_2, CF_4 T in CF_2 upright, in CF_4 inverted
13	1B	-	F	60	-	-	9/22/38 to 9/28/38	9/30/38 10/ 3/38 10/12/38 10/24/38 11/ 8/38 6/22/39	-	concord-ant	1 week	CF_2, CF_4 anterior wall type
14	2A & B	4	M	65	6/15/38	-	6/12/38	6/14/38 6/16/38 6/27/38 6/30/38	concord-ant	concord-ant	2 weeks	CF_2, CF_4 S-T depression reduced when S-T elevated in all limb leads; T in CF_2 upright, in CF_4 inverted

TABLE I—CONT'D

CASE	CLASSIFICATION SEE TABLE II	ILLUS IN FIG.	SEX	AGE	PERICARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTROCARDIOGRAMS	S-T STAGE	T STAGE	EVOLUTION OF "T_N"	S-T AND T IN CHEST LEADS
15	2A	–	M	66	5/29/40	–	5/26/40	5/29/40 5/31/40 6/ 7/40	concordant	–		CF_2, CF_4 S-T depression reduced when S-T elevated in all limb leads; T upright and tall
16	2A	–	M	65	6/15/38	–	6/12/38	6/14/38 6/16/38 6/27/38 6/30/38	concordant	discordant	–	–
17	2A	–	M	74	–	–	10/24/36	10/27/36	concordant	–	–	CF_2 S-T isoelectric, T upright
18	2A	–	F	60	–	–	12/ 9/35	12/10/35	concordant	–	–	CF_2 posterior wall type
19	2A	–	M	27	–	–	3/19/40	3/19/40 3/21/40 3/30/40 4/27/40	concordant	discordant	–	CF_2, CF_4 S-T depression reduced when S-T elevated in all limb leads; T upright and tall
20	2A & B	–	M	41	–	–	8/23/36	8/24/36 8/26/36 9/10/36 9/23/36	concordant	concordant	3 days, S-T still elevated	CF_2 S-T elevated, T upright and pointed
21	2A & B	–	F	59	–	–	9/11/36	9/12/36 9/14/36 9/25/36 10/12/36	concordant	concordant	2 weeks	CF_2 posterior wall type

22	2B	-	M	57	9/21/39	-	?	9/29/31 10/ 3/31 12/19/31	discord-ant	concord-ant	?	-
23	2B	-	M	70	-	-	12/24/31 to 12/30/31	12/30/31 1/ 1/32 1/ 3/32 1/11/32 8/17/33	-	concord-ant	1 week	CF_2 T upright
24	2B	-	M	63	-	-	?	12/17/35 12/19/35 12/31/35 5/21/36 11/12/36	-	concord-ant	?	CF_2 T upright
25	2B	-	M	49	-	-	?	1/28/37 2/ 5/37 2/23/37	-	concord-ant	?	CF_2 T upright
26	3A & B	5	M	52	6/14/36	-	6/ 9/36 and foll. days	6/13/36 6/22/36 6/29/36 7/ 5/36 7/13/36 7/20/36 6/ 2/38	concord-ant	concord-ant	5 weeks	CF_2 anterior wall type
27	3A & B	-	M	50	-	-	12/22/39	12/22/39 12/22/39 12/25/39 1/ 8/40 1/27/40 3/ 5/40 3/ 6/40	concord-ant	concord-ant	4 days S-T still elevated	CF_2, CF_4 anterior wall type

TABLE I—CONT'D

CASE	CLASSIFICATION SEE TABLE II	ILLUS. IN FIG.	SEX	AGE	PERICARDIAL FRICTION RUB HEARD	AUTOPSY	DATE OF ATTACK	DATE OF ELECTROCARDIOGRAMS	S-T STAGE	T STAGE	EVOLUTION OF "T_N"	S-T AND T IN CHEST LEADS
28	3A & B	-	F	50	-	10/18/37 Infarction of the posterior septum, posterior and lateral wall of the right ventricle, and of the anterior apex of the left ventricle, with localized fibrous pericarditis	10/ 9/37	3/12/37 10/11/37 10/13/37	concordant	concordant	5 days	CF_2, CF_4 anterior wall type
29	3A & B	-	M	34	-	-	12/16/35	12/19/35 12/21/35	concordant	concordant	5 days, S-T still elevated	CF_2 S-T elevated, T upright
30	3A & B	-	M	62	-	-	?	8/13/31	concordant	concordant	?	-
31	3A	-	M	59	-	-	12/12/35	12/23/35 12/30/35 1/ 7/36	concordant	-	-	CF_2 anterior wall type
32	3B	-	M	52	10/ 1/36	-	9/21/36	9/24/36 9/29/36 10/ 2/36 10/20/36 4/14/37	discordant	concordant	11 days	CF_2 anterior wall type
33	3B	-	M	59	-	11/21/31 Infarction of the apex and posterior wall of the left ventricle.	1929, 4/17/31 10/20/31	10/20/31 10/28/31 10/30/31	-	concordant	?	-

34	3B	–	M	56	–	–	7/30/36	8/ 1/36 8/ 4/36 8/ 7/36 8/14/36	discord-ant	concord-ant	14 days	CF_2 anterior wall type
35	3B	–	F	52	–	–	11/15/39	11/21/39 11/24/39 12/ 4/39 12/15/39 1/ 8/40 3/20/40	discord-ant	concord-ant	over 7 weeks	CF_2, CF_4 anterior wall type
36	4A & B	6	M	49	–	–	11/22/37	11/22/37 11/26/37 12/ 6/37 2/26/38	concord-ant	concord-ant	5 days, S-T still elevated	CF_2 S-T slightly elevated, T notched
37	4A	–	M	59	–	–	6/30/37	7/ 1/37 7/ 3/37 2/20/40	concord-ant	–	–	CF_2 S-T slightly elevated, T upright
38	4A & B	–	M	58	–	–	8/13/32	8/17/32 8/19/32 8/26/32 8/27/32 9/ 8/32 9/ 9/32 9/15/32 10/22/32	concord-ant	concord-ant	14 days	CF_2 posterior wall type
39	4B	7	F	44	–	–	4/ 5/39	5/ 5/39 5/ 9/39 5/22/39 7/ 1/39	–	concord-ant	?	CF_2, CF_4 posterior wall type

An analysis of the distribution of the thirty-nine cases showed that in twenty-two instances records were available in both the S-T and T

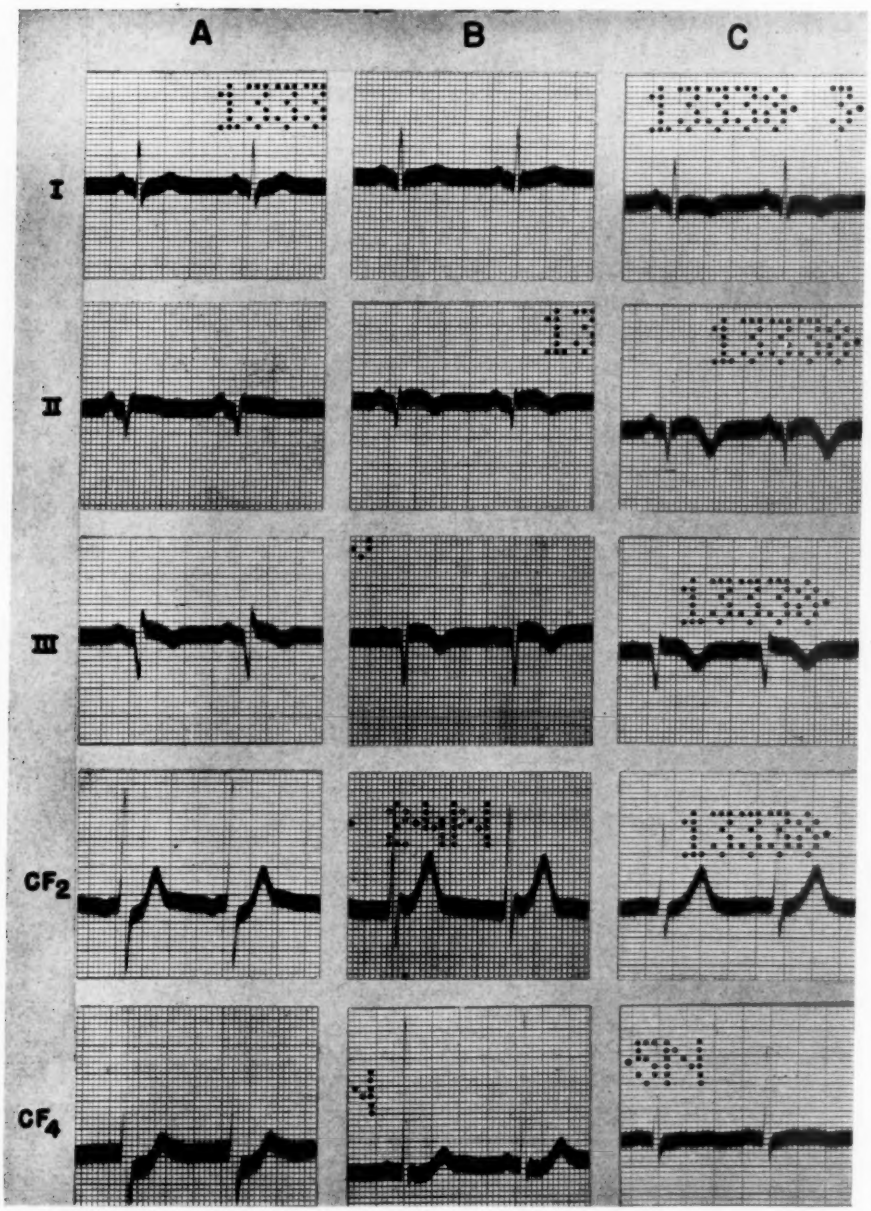

Fig. 4.—(Case 14.) The patient had the attack on June 12, 1938, and a pericardial friction rub was heard on June 15, 1938. Record *A* was taken on June 14, 1938, *B* on June 16, 1938, *C* on June 27, 1938. Record *A* shows changes of the posterior wall type, with discordant S-T changes in Leads I and III and a marked S-T deviation in the chest leads; *B* shows a concordant S-T elevation in the limb leads and the disappearance of the S-T depression in the chest leads; *C* shows a concordant T-wave inversion in the limb leads, an upright T in CF_2 and a small and inverted T in CF_4. For discussion, see text.

stages; in eight, records were obtained only in the S-T stage, and, in nine, only in the T stage. Of the twenty-two patients who were seen during both the S-T and T stages, twelve showed the criteria for special selection in both the S-T and T stages, five showed them only in the S-T, and five only in the T stage. Thus, of the thirty-nine cases, there were thirteen in which the criteria were present in the S-T stage, fourteen in the T stage, and twelve in both the S-T and T stages. The interval between the occurrence of the coronary attack and the appearance of an inverted T wave in all limb leads ("T_N," see Table I) was noted. The significance attached to this interval will be discussed later.

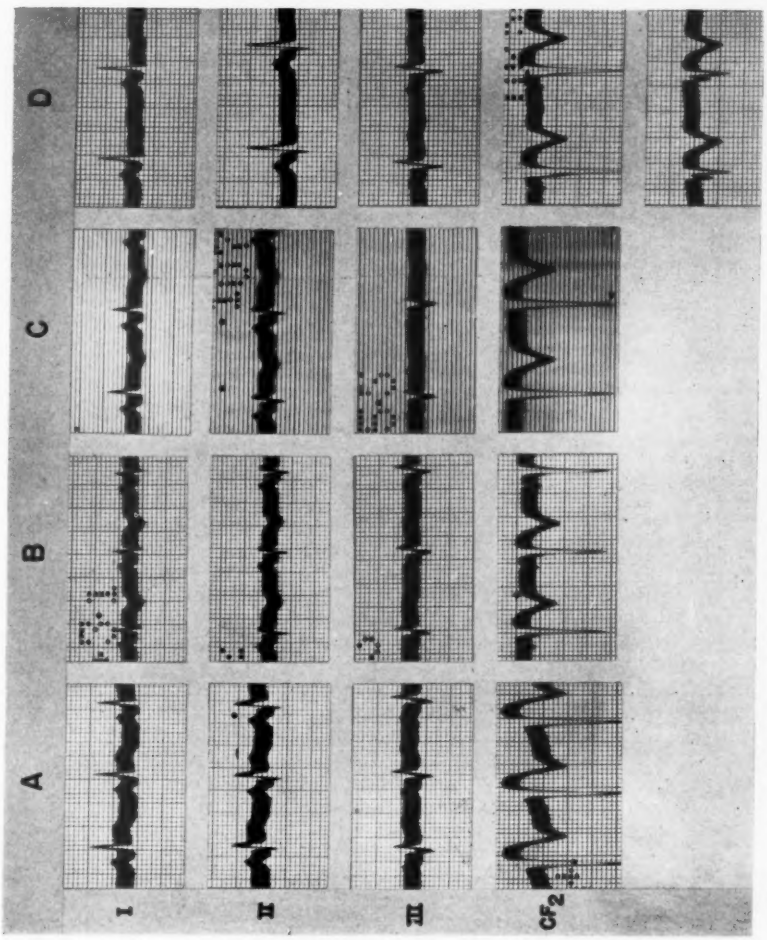

Fig. 5.—(Case 26.) The patient had several severe attacks of angina pectoris, the first on June 9, 1936; a pericardial friction rub was heard on June 14, 1936. Record *A* was taken on June 13, 1936, *B* on June 29, 1936, *C* on July 13, 1936, *D* on June 2, 1938. The electrocardiograms show QRS changes of both the anterior and posterior wall types. Record *A* shows a concordant elevation of the S-T segment in the limb leads; *C* shows a concordant T-wave inversion in the limb leads. For discussion, see text.

Of twenty-six cases in which there was T-wave inversion in the limb leads, this change occurred within two weeks after the attack in fifteen (within five days in six), and after two weeks in four. In the remaining seven cases, the time of the T-wave inversion could not be determined exactly.

TABLE II

1. Anterior wall type of myocardial infarction

A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead III, with marked elevation in Leads I and II	(a) T inverted and coronary in type in all limb leads
(b) Deep Q_1 present and/or QRS directed entirely downward in CF_2 and/or CF_4, or a deeply inverted first phase present in these chest leads	(b) ditto S-T stage
8 cases included, friction rub in 4, autopsy in 2 (cf. Figs. 1, 2)	7 cases included, friction rub in 2, autopsy in 0 (cf. Fig. 3)

2. Posterior wall type of myocardial infarction

A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead I, with marked elevation in Leads II and III	(a) T inverted and coronary in type in all limb leads
(b) a Q_3 (and Q_2) present	(b) ditto S-T stage
8 cases included, friction rub in 3, autopsy in 0 (cf. Fig. 4)	7 cases included, friction rub in 2, autopsy in 0 (cf. Fig. 4)

3. Combined anterior and posterior wall type of myocardial infarction

A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of S-T depression in Lead III (or I), with marked elevation in Lead I (or III)	(a) T inverted and coronary in type in all limb leads
(b) Q_3 (and Q_2) present, and QRS in CF_2 and/or CF_4 directed entirely downward or a deeply inverted first phase, and/or a deep Q_1 present	(b) ditto S-T stage
6 cases included, friction rub in 1, autopsy in 1 (cf. Fig. 5)	9 cases included, friction rub in 2 autopsy in 2 (cf. Fig. 5)

4. Atypical pattern of myocardial infarction

A—S-T stage	B—T stage
(a) Elevation of S-T in all limb leads, or absence of depression in Lead III (or I), with marked elevation in Lead I (or III)	(a) T inverted and coronary in type in all limb leads
(b) No special QRS pattern in limb or chest leads	(b) ditto S-T stage
(c) Evolution showing discordant changes in S-T-T in Leads I and III pointing to an anterior or posterior wall type	(c) ditto S-T stage
3 cases included, friction rub in 0, autopsy in 0 (cf. Fig. 6)	3 cases included, friction rub in 0, autopsy in 0 (cf. Figs. 6, 7)

THE RELATION OF A PERICARDIAL FRICTION RUB TO THE PRESENCE OF DIFFUSE PERICARDITIS COMPLICATING ACUTE MYOCARDIAL INFARCTION

A pericardial friction rub was heard in 11 of these 39 cases (Table I). The absence of a friction rub cannot rule out diffuse pericarditis, for in one of the two autopsy cases of diffuse pericarditis reported here no

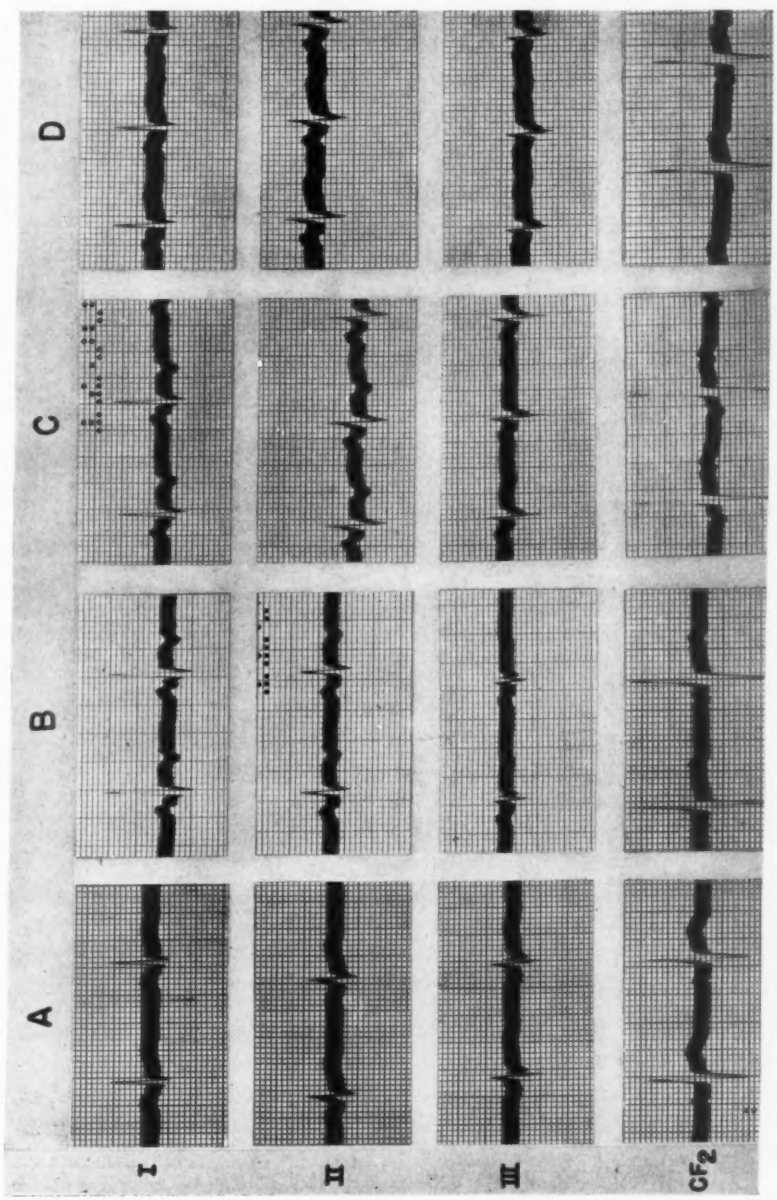

FIG. 6.—(Case 36.) The patient had the attack on November 22, 1937. Record *A* was taken on November 22, 1937, *B* on November 26, 1937, *C* on December 6, 1937, *D* on February 26, 1938. The QRS does not fit any myocardial infarction pattern. There are concordant S-T and T changes in the limb leads. Note the T-wave inversion which occurred five days after the attack, when S-T was still elevated. Discussed in text.

friction rub was detected, and it was not heard in two of four cases reported by Saphir, Priest, Hamburger, and Katz.[6] On the other hand, not every patient with myocardial infarction and an audible friction

rub can be expected to show signs of diffuse pericarditis. Thus, with an anterior wall infarct the friction rub may be evidence only of a local pericarditis superimposed on the infarcted area. An audible pericardial rub in a case of posterior wall infarction is more likely to be a sign of diffuse pericarditis. It is quite possible that the friction rub will be heard more often with more frequent observations and more careful auscultation.

S-T-T CHANGES IN THE CHEST LEADS

Since diffuse pericarditis, of itself, usually produces S-T elevation in the chest leads (Holzmann,[11] Winternitz and Langendorf,[2] Bellet and McMillan,[12] Vander Veer and Norris[13]), it would tend to exaggerate the S-T elevation in cases of anterior infarction and to reduce the S-T depression in cases of posterior wall infarction. Similarly, the tendency towards T-wave inversion in the chest leads as a later result of diffuse pericarditis would be expected to counteract, to some extent, the evolution of an upright coronary T wave in posterior wall infarction and to exaggerate the T-wave inversion in the anterior type.

Chest leads were available in thirty-three of our thirty-nine cases. In twenty-five cases CF_2 was taken, and in eight cases, both CF_2 and CF_4 were recorded. In group 1, all of the electrocardiograms, except one with an upright, pointed T wave in CF_2, were in accord with the expected pattern of the anterior wall type. Similarly, in group 2 all except one, which showed an inverted T in CF_4 (Fig. 4), were in accord with the expected posterior wall type. In group 3, in which the S-T-T configuration was unpredictable because it was the resultant of opposite tendencies due to simultaneous anterior and posterior wall infarction, the S-T-T of the chest leads was typical of anterior infarction in six cases, and of posterior infarction in one case. In group 4 the S-T-T of the chest leads was in accord with the type of infarction which was indicated by the transient, discordant S-T-T changes in the limb leads.

A discussion of the significance of these changes can best be deferred until those in the limb leads have been considered.

THE RELATION OF THE SPECIAL ELECTROCARDIOGRAPHIC PATTERN TO DIFFUSE PERICARDITIS COMPLICATING RECENT MYOCARDIAL INFARCTION

It is known that although uncomplicated, diffuse pericarditis often produces the typical concordant S-T-T changes, it occurs sometimes without characteristic changes. The absence of electrocardiographic changes, therefore, does not exclude pericarditis. This is true also of diffuse pericarditis complicating recent myocardial infarction. Examination of nineteen autopsy cases with electrocardiographic correlation, as reported in the literature and listed in Table III, reveals only eight in which the pattern selected and illustrated in the present report appears.

TABLE III

ELECTROCARDIOGRAPHIC OBSERVATIONS IN 19 CASES OF RECENT MYOCARDIAL INFARCTION ASSOCIATED WITH DIFFUSE PERICARDITIS (DIAGNOSIS CONFIRMED AT AUTOPSY)

AUTHOR	CASE	S-T STAGE	T STAGE	LOCATION OF INFARCT
Barnes[1]	1	concordant	discordant	Anterior wall of left ventricle, apex
Bohning and Katz[7]	1C*	absence of discordance	-	Septum, anterior wall and apex of left ventricle
	2B†	-	discordant	Anterior wall of left ventricle
	4A	discordant	-	Posterior wall of left ventricle
Büchner, Weber, and Haager[9]	1	absence of discordance	-	Anterior wall of left ventricle, anterior septum, apex
	9	-	discordant	Anterior and posterial wall of left ventricle, apex
Jervell[8]	17	-	discordant	Anterior and posterior wall of left ventricle
	37	discordant	-	Posterior wall, septum
	42	concordant	discord.?	Posterior wall of left ventricle
	55	discordant	-	Posterior wall of left ventricle
	56	discordant	concord.?	Anterior and posterior wall of left ventricle
Saphir, Priest, Hamburger, and Katz[6]	3	discordant	-	Lateral wall of left ventricle
	7	-	discordant	Lateral wall of left ventricle
	9	-	discordant	Anterior wall of left ventricle
	26	-	discordant	Anterior wall of left ventricle
Winternitz and Langendorf[2]	71	concordant	discordant	Posterior wall of left ventricle
	72	absence of discordance	-	Anterior and posterior wall of left ventricle
	74	discordant	-	Anterior wall of left ventricle, apex
	76	concordant	-	Lateral wall of left ventricle

*Case 2 of the present report.
†Case 1 of the present report, included because of a concordant S-T stage.

It seems significant that in all of these eight cases there were concordant changes in the S-T stage and none in the T stage. It is also significant that Weinberg and Katz' series[10] of autopsy cases of myocardial infarction with concordant changes in the T stage contains no cases of anterior or posterior infarction complicated by diffuse pericarditis. In the two autopsy cases with T-wave inversion in all limb leads which are included in their report there were multiple infarcts, but no diffuse pericarditis. Therefore, we hesitate to ascribe the concordant T-wave inversion in the cases of group 1 and 2 to the effect of complicating diffuse pericarditis and are more inclined to consider that pattern, described as "T_N type" by Weinberg and Katz,[10] together with a QRS pattern in the limb and chest leads of either of the two classical types, as reflecting extensive myocardial infarction, involving both the anterior and posterior walls.

The absence of electrocardiographic evidence in autopsy cases of recent infarction associated with diffuse pericarditis does not preclude the possibility that the presence of definite electrocardiographic changes can be taken as presumptive evidence of diffuse pericarditis. An analysis of the data assembled in this report, when coordinated with the study of autopsy material, as reported here and previously, suggests the following conclusions:

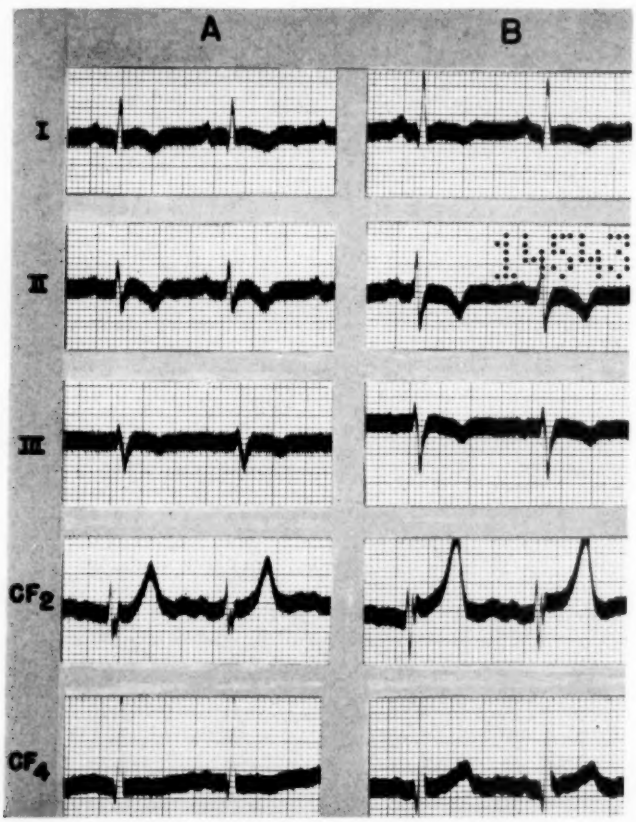

Fig. 7.—(Case 39.) The patient had the attack on April 5, 1939. Record *A* was taken on May 5, 1939, *B* on July 1, 1939. The QRS does not fit any myocardial infarction pattern. There is a concordant T-wave inversion in the limb leads. Note upright T in the chest leads, pointing to infarction of the posterior wall. Discussed in text.

1. A transient, concordant S-T stage in the limb leads in an otherwise discordant S-T-T evolution, with the QRS pattern of anterior *or* posterior wall infarction (groups 1 and 2), is highly suggestive of accompanying diffuse pericarditis.

2. A concordant T-wave stage in the limb leads is suggestive of extensive infarction, especially when this pattern develops within a week, while the elevation of the S-T segment is still present. However, further anatomic correlation studies are necessary to evaluate the role of diffuse pericarditis in producing the pattern of concordant T-wave inversion in simple infarction.

3. In the presence of the QRS changes of both anterior and posterior infarction in the limb and chest leads, and of concordant S-T-T changes in the limb leads (group 3), no statement can be made as to the presence or absence of diffuse pericarditis.

4. In the absence of any QRS pattern of infarction in the limb and chest leads, and with the presence of concordant S-T-T changes in the limb leads (group 4), the evolution of a tall, upright T wave in the chest leads indicates infarction and differentiates the record from one of uncomplicated diffuse pericarditis.

As a result of these deductions, the number of cases in which it can be presumed that there is a complicating diffuse pericarditis is more limited. If the ten cases of group 3 are discounted, since the involvement of both the anterior and posterior walls may account for the concordant S-T-T changes in the limb leads, there remain twenty-nine of the original series of thirty-nine cases with an electrocardiographic pattern of infarction which possibly reflects a complicating diffuse pericarditis. In seventeen of these twenty-nine cases there was a concordant T stage, and this, judging from the post-mortem evidence, may be assumed to be the result of extensive myocardial infarction. This is particularly true of the three cases with the unexpected T-wave inversion which occurred within five days after the attack, for pericarditis, per se, does not lead to T-wave inversion until weeks after the early S-T stage (Winternitz and Langendorf[2]). Thus, after careful analysis, in only twelve (3.2 per cent) of the series of 380 cases of recent myocardial infarction can an electrocardiographic diagnosis of simple infarction associated with diffuse pericarditis be justified. Since the diagnosis is based mainly on a transient change during the S-T stage of the electrocardiographic evolution caused by the infarction, it seems likely that many cases may have been missed because no records were taken at the time when this change was present. The greater statistical frequency of complicating diffuse pericarditis at autopsy would bear this out. The electrocardiographic diagnosis of diffuse pericarditis complicating recent myocardial infarction will be made with greater frequency only when electrocardiograms are made more often during the S-T stage of infarction.

SUMMARY AND CONCLUSIONS

1. Out of 380 consecutive cases of recent myocardial infarction, thirty-nine presented a limb lead pattern of concordant S-T elevation or concordant T-wave inversion which fulfilled the criteria for the diagnosis of complicating pericarditis as formulated by Barnes.

2. Both QRS and S-T-T changes in the limb and chest leads have to be taken into account and studied in their relation to each other, if uncomplicated diffuse pericarditis is to be differentiated electrocardiographically from myocardial infarction and from myocardial infarction complicated by diffuse pericarditis.

3. Autopsy control in four cases of the present report, post-mortem correlation in previous reports of cases of recent myocardial infarction with diffuse pericarditis, autopsy observations in cases of infarction with the "T_N type" of electrocardiogram, and electrocardiographic correlation in autopsy cases of recent myocardial infarction with diffuse pericarditis lead to the following conclusions:

(a) A transient, concordant S-T elevation in the limb leads in an otherwise discordant S-T-T evolution in cases of anterior or posterior wall infarction is highly suggestive of a complicating diffuse pericarditis.

(b) A concordant T-wave inversion in the limb leads, with QRS changes in the limb and chest leads of either the anterior or posterior wall type, is caused by extensive myocardial infarction, and cannot be considered a result of simple infarction complicated by diffuse pericarditis. However, further anatomic correlation studies are necessary to substantiate this statement.

4. As a result of these deductions, in only twelve (3.2 per cent) of the present series of 380 cases of recent myocardial infarction could a diagnosis of complicating diffuse pericarditis be made. Serial electrocardiograms during the S-T stage of infarction should make the percentage of electrocardiographic diagnoses of complicating diffuse pericarditis more nearly approach the post-mortem incidence (15.3%).

I am deeply indebted to Dr. L. N. Katz for his advice and criticism in the preparation of this report.

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THE FREQUENCY OF ELECTROCARDIOGRAPHIC VARIATIONS IN NORMAL, UNANESTHETIZED DOGS

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THE observation that T waves not infrequently may be inverted in all three leads in normal dogs was first made by Smith.[1] Attention was directed to the extreme variability in the T waves of normal dogs, as contrasted to the T waves of normal human subjects, by Barnes and Mann,[2] who concluded that, unless the direction of the T wave had been established under normal conditions in dogs, conclusions drawn following ligation of the coronary arteries might prove confusing. Katz, Soskin, and Frisch[3] studied serial electrocardiograms in normal, unanesthetized dogs over periods of four months and concluded that the variability in the T waves was caused by the relative mobility of the dog's heart. These authors suggested that, previous to experimental electrocardiographic studies on dogs, serial records over a period of days were indicated. Harris and Hussey[4] reported on the frequency and direction of T-wave variations in seventy-five records on fifty normal dogs. Gross and Calef[5] found that their normal records showed the T-wave variations which had been reported by the previous workers.

Numerous statements have been made in the literature to the effect that electrocardiograms taken on dogs differ in some respects from human records, and that electrocardiograms which are considered pathologic in man may be observed fairly frequently under normal circumstances in the dog. Since the dog continues to be the most frequently used animal in experimental electrocardiography, data on the variation of individual complexes in normal dogs are of sufficient importance to be enlarged upon. We believe that a further addition to our knowledge of T, Q, and S wave variations in normal dogs, as to their frequency and some other minor changes not mentioned previously, is needed.

METHOD

Healthy, adult dogs were trained to lie on either their right or left side, so that they were relaxed and flat on the table while the record was being taken. Animals which could not be trained to relax on the table were not used in this study. On five dogs records were made while they lay first on one side, and then on the other, in order to ascertain the effect of change of position on the electrocardiogram. From two to seventeen records were taken on each animal within four weeks' time. The records were standardized so that one millivolt produced a deflection of one centimeter.

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RESULTS

The data have been arranged in tabular form so that the variations and the frequency with which they occurred might be observed in each animal. A total of 218 records on twenty-four normal dogs were obtained.

Occurrence of Variations in the Various Complexes (Table I).—P waves are almost always present in normal dogs. A variation in the amplitude of the P wave in any one lead was usually associated with sinus arrhythmia. This occurred in sixteen instances in Lead II, and 12 times in Lead III. Whenever a change in the amplitude or direction of the P wave occurred, the animal was usually apprehensive or excited. P-wave inversion was observed in Leads I and III, but never in Lead II.

Study of the Q waves and inverted T waves in all three leads revealed that when there was a Q wave in Lead I the T wave in that lead was likely to be inverted. This was not the case in Leads II and III. The amplitude of the Q wave was found to be important, because whenever it was greater than 4 mm. the following T wave was inverted in over 90 per cent of the cases, and this was true of all three leads. This relationship between deep Q waves and inverted T waves was especially apparent in Lead I; when T shifted from an inverted position to an upright one, the Q wave would either disappear or become very small. The Q waves were deepest and most frequently found in Lead II.

The data reveal an interesting relationship between the presence of S waves and upright T waves. S waves were least frequent in Lead I, as were upright T waves. In Leads II and III the S waves were more frequent, and so were upright T waves. In Lead III, in which S waves occurred most frequently, upright T waves were most common. Just as a Q wave is likely to be followed by an inverted T wave, so, when an S wave is present, upright T waves will usually be found in any lead, especially Lead III. S waves were usually deepest and most frequently encountered in Lead III. The relationship between upright T waves and deep S waves in Lead III does not appear to be a close one, because S_3 is not as likely to change as Q_1 when there is a reversal in the direction of the T wave in these leads.

Contrary to a prevalent idea, as was first pointed out by Harris and Hussey, inverted T waves preponderate in Lead I, whereas upright T waves are the most frequent in Lead III. Although there is apparently a reciprocal relationship between T_1 and T_3, it is not necessarily true that an inverted T_1 will be accompanied by an upright T_3, or vice versa.

Minor RS-T deviations, seldom exceeding 1 mm., were found most frequently in Lead II. No correlation could be established between RS-T deviation and inverted or upright T waves.

Further Analysis of the Data in Table I.—Reversal in the direction of the T wave occurred in nineteen out of twenty-four dogs. These reversals were more frequent in Leads I and II. Inversion of the T wave

in all three leads was less frequent; it was observed in seven out of the 24 dogs in our series. Applying Pardee's criteria to Q_3, we found that Q_3 exceeded 25 per cent of the tallest R wave in nine records. Deep S waves were larger than 25 per cent of the tallest R wave in ten records.

Since Q and S waves were found to be related to T waves, it was considered important to analyze the data for the occurrence of Q and S waves in the same lead. It was found that the two occurred least frequently together in Lead I and most frequently in Lead III. In those instances in which both were present in Leads I and III, usually either the Q or the S wave measured one millimeter or less. In Lead II, however, it was not uncommon to find both Q and S waves which measured more than two millimeters.

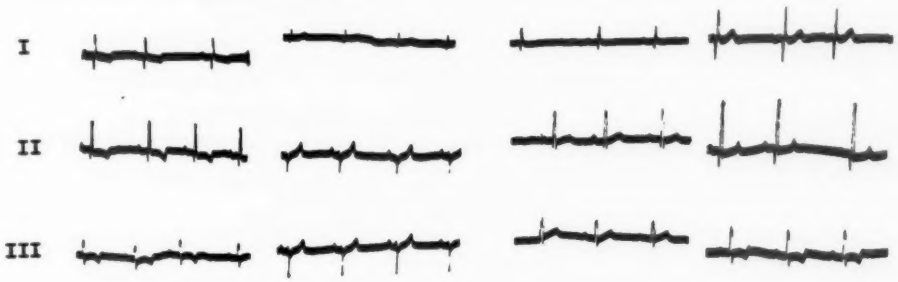

Fig. I Fig. II Fig. III

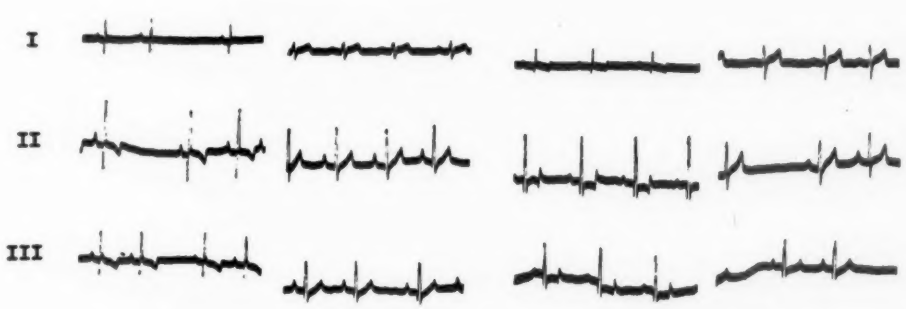

Fig. IV Fig. V Fig. VI

Fig.—*I*, Note inverted T waves in all three leads, also Q_1 and Q_2. *II*, An example of marked left axis deviation in a presumably normal dog. *III*, Tracings from the same animal on different days. Note deepening of Q_1 and increased amplitude of T_1; this is rare; such a deep Q is usually associated with an inverted T (Compare with IV). Observe deepening of S_3 and reversal of T_3 in the second record. This combination is also unusual. *IV*, Note association of a deep Q with an inverted T in Leads II and III. This is usual when Q is present and equal to 25 per cent or more of the tallest R. *V*, S_2 is more than 25 per cent of tallest R. Note that all T waves are upright, which is common when a large S is present in any lead, though not invariable. *VI*, Tracings from the same animal on different days. Note reversal of T_1, disappearance of Q_1, and appearance of a deep S_1 in the second record. Note RS-T depression in the record for the first day, Leads I and II.

The electrical axes were determined by Dieuaide's method[6] in ten dogs which had ten or more records taken. Out of each group of records three

TABLE I

DOG NUMBER	NUMBER OF RECORDS TAKEN	P WAVES			Q WAVES			S WAVES			T WAVES												RS-T		
		L_1	L_2	L_3	L_1	L_2	L_3	L_1	L_2	L_3	L_1				L_2				L_3				L_1	L_2	L_3
											↓	↑	→	∫	↓	↑	→	∫	↓	↑	→	∫			
1867	10	10	10	10	9	10	9	1	0	0	8	1	0	1	2	1	0	6	0	5	0	4	0	1	1
L.F.	11	10	10	10	9	9	5	1	0	0	6	1	0	3	1	4	0	4	0	9	0	2	0	1	0
L. 3	9	9	9	9	9	9	0	0	0	0	5	1	0	3	0	6	0	3	0	9	0	0	0	0	0
L. 1	10	8	10	10	7	9	1	1	8	8	4	0	0	5	0	9	0	1	0	10	0	0	0	0	0
1887	10	10	10	6	10	10	10	1	2	10	9	0	0	1	6	3	0	1	2	6	0	2	0	0	0
1885	10	10	10	10	9	10	10	0	0	0	5	3	0	0	7	0	0	3	5	0	0	5	0	1	0
1880	16	16	16	16	16	16	16	8	16	15	16	0	0	0	16	0	0	0	15	0	0	0	0	14	8
1889	10	9	10	10	9	6	2	0	4	10	1	7	0	0	0	9	0	1	0	9	0	1	0	0	0
June P.	12	11	12	12	2	4	12	10	12	10	1	10	0	1	0	10	0	2	0	9	0	3	0	0	7
F.B.	3	3	3	3	0	0	3	3	3	3	0	2	0	0	0	3	0	0	0	1	0	2	0	0	2
C.A.	13	13	13	13	12	13	6	0	0	8	7	3	0	3	0	12	0	1	0	13	0	0	0	3	0
1866	11	11	11	11	8	9	11	0	11	11	4	4	3	0	2	4	1	4	2	1	0	7	0	0	0
1882	2	2	2	2	2	2	2	0	0	0	0	1	1	0	1	1	0	0	1	0	0	1	0	0	0
1881	3	3	3	3	3	3	3	0	3	3	3	0	0	0	0	0	0	3	2	0	0	1	0	2	0
1886	5	3	5	5	5	5	4	0	2	3	2	1	1	1	1	1	0	3	0	2	0	3		3	1
1888	3	3	3	3	3	3	2	0	2	2	0	1	0	2	0	1	0	2	1	2	0	0	0	1	0
F.W.	3	3	2	3	0	0	3	2	3	3	1	2	0	0	3	0	0	0	3	0	0	0	0	0	0
1863	17	17	17	17	17	17	16	0	2	17	17	0	0	0	16	1	0	0	0	15	0	2	0	0	0
1873	17	17	16	17	13	14	12	11	13	17	9	1	2	4	6	3	0	7	4	9	0	4	0	0	0
1864	10	10	10	10	8	6	7	0	1	9	8	2	0	0	9	1	0	0	7	1	0	2	0	1	0
1865	10	8	10	10	8	10	10	1	5	9	6	2	1	0	2	5	0	1	0	7	0	2	0	0	0
L.H.C.	8	7	8	8	0	7	8	8	6	6	6	2	0	0	0	8	0	0	2	6	0	0	0	0	0
Whitey	8	6	7	8	4	5	5	0	6	8	3	0	0	4	1	3	0	3	2	3	0	3	0	0	0
Blackie	7	4	5	4	5	5	3	2	3	3	1	3	1	0	1	2	0	2	0	2	0	1	0	0	0
24 dogs	218	203	212	210	166	183	155	49	102	157	122	43	9	32	74	77	1	47	46	199	0	44	0	27	19

The numbers appearing under L_1, L_2, and L_3 represent the frequency of occurrence of the wave indicated in the lead designated.

The symbols ↓ ↑ → ∼ indicate inverted, upright, isoelectric, and diphasic, respectively.

The figures under RS-T (L_1, L_2, L_3) indicate the number of times deviation of the RS-T segment was observed in the lead indicated. At least one millimeter deviation was required to qualify for tabulation.

TABLE II

DOG NUMBER	NUMBER OF RECORDS STUDIED	REVERSAL IN DIRECTION OF T WAVES			INVERTED T WAVES, ALL LEADS	Q_3 EXCEEDS 25% TALLEST R COMPLEX	S_2 EXCEEDS 25% ALL R COMPLEXES	PRESENCE OF Q AND S COMPLEXES AT SAME TIME		
		L_1	L_2	L_3				L_1	L_2	L_3
1867	10	3	3	0	0	0	0	0	0	0
L.F.	11	3	1	0	0	1	0	0	1	0
L.3	9	1	0	0	0	0	0	0	0	3
L.1	10	1	0	0	0	0	0	0	5	0
1887	10	3	3	2	2	0	0	0	11	10
1885	10	1	2	3	5	6	0	3	1	3
1880	16	0	0	0	15	0	0	10	16	14
1889	10	1	0	0	0	0	3	0	0	0
June P.	12	2	0	0	0	0	0	0	6	11
F.B.	3	0	0	0	0	0	0	0	0	3
C.A.	13	3	0	0	0	0	1	0	0	3
1866	11	2	3	1	0	0	1	0	8	6
1882	2	0	1	1	0	0	0	0	1	1
1881	3	0	0	0	0	0	0	0	2	1
1886	5	2	2	0	0	0	1	0	2	2
1888	3	0	0	0	0	0	1	0	2	2
F.W.	3	2	0	0	1	0	0	0	0	2
1863	17	0	2	0	0	0	0	1	3	15
1873	17	1	3	4	0	0	2	2	9	6
1864	10	5	2	3	4	0	0	0	0	0
1865	10	6	2	0	0	0	0	0	5	6
L.H.C.	8	1	0	1	0	2	0	0	4	4
Whitey	8	3	1	1	1	0	0	0	4	2
Blackie	7	2	2	0	0	0	1	0	2	3
Total	218	42	27	17	28	9	10	16	82	97

The third column of figures (reversal in direction of T waves) records how many times an upright T wave became inverted, or vice versa, in the series of records from the animal identified in column one. The other column headings are self-explanatory.

which showed the greatest degree of variation were chosen. The greatest variation observed in any one animal was 75 degrees; the axis shifted from minus 65 degrees to plus 10 degrees. Over 60 per cent of the recorded axes fell between 50 degrees and 75 degrees. The usual shift in axis from day to day in the majority of the animals was less than 15 degrees.

We found no consistent correlation between electrocardiographic variations and the side the animal was lying on. T-wave reversals did not necessarily follow changes in the electrical axis.

One animal, dog 89, consistently had an electrocardiogram unlike those of the other animals. As this animal's electrocardiogram was so constantly different in over twenty-five records, we are publishing it as an example of marked left axis deviation in a normal dog.

SUMMARY

Two hundred eighteen electrocardiograms were made on twenty-four normal dogs.

Under normal conditions the P waves showed changes in direction and amplitude in the same lead. Since these changes happened more frequently in nervous or excited animals with sinus arrhythmia, we suggest that they may be associated with vagal or sympathetic nervous influences. Changes in amplitude and reversal of direction of the T waves are tabulated to illustrate the variability in this complex which has been reported previously. A change in the amplitude or disappearance of Q and S waves is the next most frequent variation in the electrocardiograms of normal dogs. Even though variations do occur in the various complexes in different animals, each dog's records are characteristic for that animal. Slight RS-T deviations from the isoelectric line occurred, but seldom exceeded one millimeter. There was a relationship between Q waves and inverted T waves in Lead I which was observed in 78 per cent of the records in our series. Likewise, there was a relationship between S waves and upright T waves in Lead III; this was observed in 75 per cent of the records. Apparently, therefore, there is a reciprocal relation between Q waves and inverted T waves in Lead I, and between S waves and upright T waves in Lead III.

Extrasystoles occurred only once in this series of trained animals, and "dropped ventricular beats" were observed in less than 2 per cent of the records.

We wish to thank Dr. R. H. Major for his help, suggestions, and criticisms.

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THE INCIDENCE OF RHEUMATIC AND CONGENITAL HEART DISEASE AMONG SCHOOL CHILDREN OF LOUISVILLE, KY.

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THE variation in the geographic distribution of rheumatic heart disease among the school children of the United States has been emphasized by numerous observers. All are in accord that the disease is much less frequent in the South than in the North. Paul and Dixon,[1] in a survey of rheumatic heart disease among American Indian school children in Southern and Northern reservations, found an incidence of 0.5 per cent in the former, and 4.5 per cent in the latter, group. This study has especial significance because both surveys were made by the same examiners. Sampson, Christie, and Geiger,[2] of San Francisco, have reviewed the literature on the incidence of rheumatic heart disease in the school populations of the middle, western, and eastern United States; they stressed the marked geographic differences of the disease, and found that San Francisco school children showed the lowest incidence, i.e., 0.22 per cent. In a more recent survey, Rauh[3] found in Cincinnati an incidence similar to that in San Francisco. Of 85,389 school children, 0.2 per cent had rheumatic heart disease. Statistics on the geographic distribution of congenital heart disease are not as reliable because the majority of the surveys assumed that 20 per cent of organic heart disease in children is congenital. This is a false assumption.

The present report is a study of the incidence of rheumatic and congenital heart disease in the school children of Louisville.

Louisville, situated on a plateau about 60 feet above the Ohio River at an ordinary stage of water, is in latitude 38° 15′ N, and longitude 85° 45′ W. It is 449 feet above sea level. The terrain is undulating, with good drainage. The 1930 census showed a population of 307,745 in an area of 37.88 square miles. The population is composed of 251,364 native whites, 8,938 foreign-born whites, and 47,354 negroes. The mean annual temperature is 63.1° F., the mean annual maximum, 78.5° F., and the mean annual minimum, 34.5° F. The mean relative humidity is 76 per cent in the morning and 62 per cent in the afternoon. There is an average of 124 days of rainfall, with an average annual precipitation of 43.49 inches. The average annual snow precipitation is 29 inches. Clear days number 128, cloudy days, 109 and partly cloudy, 128.

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METHOD OF STUDY

The school physicians connected with the Department of Health of the City of Louisville each year examine all the pupils who attend the kindergarten, first, fourth, and seventh grades, and the first year of the junior high school. Therefore, all the children in the entire school system are examined at least once in three years. Examinations are made with the chest exposed. The school physicians do not attempt to make an etiologic classification of the cardiac abnormalities which they find. Under the heading of "heart" on the child's health card, a notation is made as to any deviation from the presumed normal, and the child is then referred to the family physician for further examination. For three consecutive school years, from 1936 through 1939, all children designated "heart" in each school, public and parochial, were re-examined by myself. Children who were receiving bedside instruction because of home confinement as a result of heart disease were checked through the Board of Education. The cases of pupils who died in the public hospitals during the years of the survey were included in the total number analyzed. The criteria for the diagnosis of rheumatic and congenital heart disease, as specified by Paul and his associates,[4] were followed, except that apical systolic murmurs were ignored unless they were accompanied by cardiac enlargement, or were very loud and heard over a wide area of the precordium. In borderline cases the children were re-examined several times during the three years of the study. Roentgenologic and electrocardiographic facilities were rarely available.

A yearly average of 41,905 children from 6 through 14 years of age attended the public and parochial schools from 1936 through 1939. A total of 221, or 0.52 per cent, had rheumatic or congenital heart disease (Table I). There were 35,713 white children, of which number 196, or 0.54 per cent, had these etiologic types of heart disease. Of 6,192 negro children, 25, or 0.45 per cent, had rheumatic or congenital lesions. Rheumatic heart disease was present in 153, or 0.36 per cent, and congenital defects in 68, or 0.16 per cent. Thus, rheumatic heart disease accounted for 69 per cent of the 221 cases of organic heart involvement. Of the 153 cases of rheumatic heart disease, 131 occurred in white children. This is an incidence of 0.33 per cent. The incidence in negro children was the same, 0.35 per cent (twenty-two cases). The incidence of congenital heart disease was greater among the white than among the colored children. Only three, or 0.05 per cent, of the negro children had congenital lesions, in contrast to sixty-five, or 0.18 per cent, in the white pupils.

Rheumatic heart disease was approximately equally common in both sexes of both races (Table II). Rheumatic valve lesions were present in sixty-six white boys, sixty-five white girls, twelve negro boys, and ten negro girls. Congenital heart disease was found in twenty-six

TABLE I

DISTRIBUTION AS TO RACE OF RHEUMATIC AND CONGENITAL HEART DISEASE AMONG 41,905 SCHOOL CHILDREN

RACE	NUMBER OF CHILDREN	RHEUMATIC		CONGENITAL		TOTAL NUMBER ORGANIC HT. DIS.	
		NO.	%	NO.	%	NO.	%
White	35,713	131	0.33	65	0.18	196	0.54
Negro	6,192	22	0.35	3	0.05	25	0.45
Total	41,905	153	0.36	68	0.16	221	0.52

white boys, thirty-nine white girls, three negro boys, and no negro girls. The sex distribution of all the school children was approximately equal in both races.

TABLE II

DISTRIBUTION AS TO RACE, AGE, AND SEX OF RHEUMATIC AND CONGENITAL HEART DISEASE

AGE	RHEUMATIC (153 CASES)						CONGENITAL (68 CASES)					
	WHITE			NEGRO			WHITE			NEGRO		
	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL	M	F	TOTAL
6- 7	1	4	5	1	0	1	8	12	20	0	0	0
7- 8	1	1	2	1	0	1	5	5	10	1	0	1
8- 9	4	5	9	1	0	1	3	2	5	0	0	0
9-10	2	6	8	1	0	1	2	1	3	1	0	1
10-11	3	7	10	2	2	4	2	2	4	0	0	0
11-12	6	6	12	4	3	7	1	3	4	0	0	0
12-13	12	8	20	0	1	1	1	3	4	0	0	0
13-14	10	8	18	0	0	0	2	3	5	0	0	0
14-15	27	20	47	2	4	6	2	8	10	1	0	1
Total	66	65	131	12	10	22	26	39	65	3	0	3

An attempt was made to ascertain the social distribution of the rheumatic cases. Despite overlapping of economic levels in many of the schools, there was a greater incidence of rheumatic heart disease among the children from the "poorer" districts than from the "better" districts of the city. However, the incidence was not significantly higher in the recent slum clearance areas of the city.

DISCUSSION

The incidence of rheumatic heart disease in Louisville school children is similar to that in San Francisco[2] and Cincinnati.[3] The fact that 69 per cent of the cases of organic heart disease were rheumatic confirms the observations made in those communities that the incidence of rheumatic heart disease in children cannot be ascertained on the assumption that 80 per cent of the murmurs in children are of rheumatic origin.

There is a divergence in the reports as to the racial incidence of rheumatic heart disease. Rauh[3] found that the incidence of acquired heart disease was almost twice as high among colored as among white children. Others[5, 6] have reported a higher incidence in white children. This study did not reveal any racial difference in incidence.

No attempt was made to make a careful anatomic diagnosis of the lesions encountered, but it is of interest that there was only one case of dextrocardia and not a single instance of complete heart block.

No cases of rheumatic or congenital disease were encountered in siblings.

The fact that the incidence of rheumatic heart disease was not significantly higher in the slum clearance areas of the city would indicate, as others have noted, that rheumatic fever is not strictly a disease of paupers.

SUMMARY

1. A study is presented of the incidence of rheumatic and congenital heart disease among 41,905 school children from 6 through 14 years of age who yearly attend the schools of Louisville, Ky.

2. A total of 221, or 0.52 per cent, had rheumatic or congenital heart lesions; this included 0.54 per cent of the white and 0.45 per cent of the negro children.

3. Rheumatic heart disease accounted for 69 per cent of the 221 cases.

4. Rheumatic heart disease occurred in 0.33 per cent of the white and 0.35 per cent of the negro pupils.

5. Congenital heart lesions were found in 0.18 per cent of the white and 0.05 per cent of the negro children.

6. Rheumatic valve lesions were approximately equally common in both sexes of both races. No cases were encountered in siblings.

7. Although the incidence was not higher in the slum clearance areas of the city, there was a greater incidence of rheumatic lesions in children from the "poorer" than from the "better" districts.

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OBSERVATIONS ON THE PRODUCTION OF MYOCARDIAL DISEASE WITH ACETYLCHOLINE

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HALL, et al.,[1, 2] have reported that they were able to produce severe myocardial and coronary artery damage, resulting in myocardial failure, in six out of eight dogs, using injections of a 1:10,000 solution of acetylcholine, administered intravenously over a period of one and one-half hours daily. Their animals developed cardiac symptoms and died of heart failure after 19 to 227 consecutive daily injections. Cardiac murmurs first appeared in their older dogs after 12 to 19 injections, and in the younger ones murmurs were noted after 34 to 136 injections. In the hearts at autopsy they found areas of hyalinization, with developing fibrosis, hyaline degeneration of the media of medium and smaller sized arteries, with fibrosis, recent infarcts of the myocardium, thrombosis of many branches of the coronary arteries, recanalization of occluding thrombi, fatty degeneration of the myocardium about infarcted areas, and large areas of fibrosis. These changes were noted only in the old dogs. In the young animals they found no arterial changes, but reported mild to severe hyaline degeneration of the myocardium, a few scattered hemorrhagic areas with cellular infiltration, and very recent infarcts of the papillary muscle. The authors attributed the effect to a prolonged parasympathetic overbalance of the autonomic nervous system, and to confirm this hypothesis they reported similar lesions in dogs that had been adrenalectomized[3] and in other animals after continuous electrical stimulation of the vagi.[4]

In undertaking an experimental study of "chronic myocarditis," an attempt has been made to produce myocardial and coronary artery damage, following, with certain modifications, the method described by Hall, et al.

METHOD

Four male and four female dogs of mixed breeds, ranging in weight from 8 to 22 kg., were selected. D5 was young, D6 very old, and the remaining six animals were middle-aged. Injections, under sterile precautions, were begun after a preliminary period of observation and training. The technique described by Hall was used, both for preparing the concentrated acetylcholine solution (each c.c. contained 25 mg.), and for the daily injections, with the exception that the concentrated acetylcholine hydrobromide (Eastman) was given in 250 c.c. of normal saline instead of 500 c.c., and the unanesthetized animals were injected only six days a week. The prescribed dose of 50 mg. of acetylcholine per dog, regardless of size, was given each day, at the outset. Such a dose produced no noticeable cardiac response after the initial tachycardia had subsided. Consequently, the

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amount was soon increased sufficiently to attain a maximum cardiac effect throughout the ninety-minute period. (A tachycardia of over two hundred beats per minute was maintained if at all possible.) No standard dose was given because of the wide variation in the tolerance of the individual animals. The use of a buffered concentrated solution of acetylcholine was also discontinued because the compound was relatively unstable when in solution; thereafter, the crystalline material, in accurately weighed amounts, was added directly to the saline solution just before starting the infusion.

The heart rate and rectal temperature were recorded before starting each injection, and during the infusion the heart rate was checked at ten-minute intervals. Electrocardiograms, the femoral artery blood pressure, and blood cell counts were taken from time to time during the series of injections. Each animal was weighed at weekly intervals.

After two animals had been given sixty injections, two ninety injections, and four 100 injections, a blood culture, electrocardiogram, roentgenogram of the heart, and complete blood cell count were obtained on all of the animals. Measures were then taken to produce acute dilatation of the heart, first, by massive intravenous infusions of normal saline at a rapid rate, and, second, by vigorous, exhausting exercise.

Following a subsequent rest period of four months, an electrocardiogram and roentgenogram of the heart were again taken on each dog. One of the animals that had received 100 injections, D3, was sacrificed. Of the remaining animals, two, D4 and D7, were allowed to become pregnant; the rest were given a second course of injections. In this series three dogs survived 127 injections and were then sacrificed.

At autopsy, all arteries of the thorax and abdomen which were large enough to admit the tip of a pair of fine scissors were opened and examined. The coronary vessels were opened and inspected before the fresh heart was cleaned and weighed. Sections were taken routinely from both auricles, the interauricular septum, the right and left ventricular walls, the apex, the papillary muscles, the valves, and the interventricular septum, as well as from the lung, liver, kidney, pancreas, spleen, intestine, adrenal gland, and skeletal muscle. Similar sections from a number of normal hearts were studied for comparison.

TABLE I

DOG	WEIGHT	SEX	FIRST SERIES OF INJECTIONS			SECOND SERIES OF INJECTIONS		
			NO.	DAILY DOSE INCREASED FROM	AVERAGE DAILY DOSE	NO.	DAILY DOSE INCREASED FROM	AVERAGE DAILY DOSE
	kg.			*mg.**	*mg.*		*mg.*	*mg.*
1	24	M	100	50 to 800	260	56	300 to 500	420
2	14	F	101	50 to 500	240	89	100 to 250	150
3	24	M	100	50 to 1000	360	--	--	--
4	17	F	90	50 to 1100	445	4	500 to 600	535
5	23	M	100	100 to 1000	420	127	250 to 500	415
6	22	M	91	75 to 800	320	125	250 to 500	385
7	17	F	60	100 to 600	280	--	--	--
8	8	F	60	100 to 800	325	126	200 to 500	370

*Mg. of acetylcholine necessary to maintain a heart rate of 200 beats per minute throughout the 90-minute injection period.

RESULTS

The essential data are presented in Tables I and II. It is to be noted that cardiac murmurs were produced in only two of the eight dogs. In D4 it appeared after twelve injections, and, in D7, after forty-six injections. Both dogs were pregnant at the time. The systolic mur-

TABLE II

DOG	TOTAL NO. OF INJECTIONS	CARDIAC MURMURS APPEARED	SIGNS OF HEART FAILURE	AURICULAR FIBRILLATION PRODUCED	P-R INTERVAL (SEC.)	OTHER EKG CHANGES	CAUSE OF DEATH	HISTOLOGIC EVIDENCE OF SCLEROSIS	MYOCARDIAL INFARCTIONS	HW/BW RATIO*
1	156	No	No	Frequently	0.12	None	Ventricular Fibrillation	None	None	0.0074
2	190	No	No	Frequently	0.08	None	Ventricular Fibrillation	None	None	0.0066
3	100	No	No	Rarely	0.12	None	Sacrificed	None	None	0.0060
4	94	After 12 Injections	Yes	Never	0.12	M-shaped QRS_2 Elevated ST_{2-3}	Pneumonia and Cardiac Failure†	None	None	0.0075
5	227	No	No	Rarely	0.12	None	Sacrificed	None	None	0.0069
6	216	No	No	Occasionally	0.10	Depressed ST_{2-3}	Sacrificed	None	Small area in papillary muscle, old	0.0053
7	60	After 46 Injections	No	Frequently	0.12	None	Pneumonia	None	None	0.0057
8	186	No	No	Rarely	0.10	None	Sacrificed	None	Old area in papillary muscle of L. V.	0.0088

*$\frac{\text{Fresh total heart weight}}{\text{Body weight}} = 0.00798$, with a minimum of 0.00600 and a maximum of 0.00994.[5]

†Primarily failure of the right ventricle, caused by tricuspid insufficiency.

mur in D4 persisted and increased in intensity, whereas the murmur of D7 disappeared during the four-month rest period. None of the animals died of cardiac failure. Two dogs (D1, after 156 injections, and D2, after 189 injections) died suddenly while being infused, presumably as a result of ventricular fibrillation, for both of them had auricular fibrillation just prior to death. These two animals had auricular fibrillation during almost every injection, whereas only rarely did any of the others, with the exception of D7, develop fibrillation. Pneumonia was the cause of two deaths. The remaining four were sacrificed. Throughout the study, all the dogs seemed to be in good health; they gained weight and enjoyed normal activity. The acute effects which were noted during the daily acetylcholine infusions were identical with those described by Hall, i.e., tachycardia, lacrimation, salivation, vomiting (no hematemesis, however), and diarrhea, usually with melena; and, when the amount of acetylcholine per minute was increased to the maximum tolerance of the animal, extrasystoles, dropped beats, auricular fibrillation and flutter, as well as marked dyspnea (even apnea), were observed. There was no roentgenologically demonstrable increase in the size of the heart except in the case of D4, in which a 12 per cent enlargement was found. The electrocardiograms remained essentially unchanged throughout the entire period. In no instance did the P-R interval measure more than 0.14 second. At the conclusion of the first series of injections, *Staphylococcus albus* was grown from the blood of D4. No cultures were taken on the surviving dogs at the conclusion of the second series of injections.

MORPHOLOGIC CHANGES

Heart.—The hearts of six of the animals were grossly normal. The $\frac{HW}{BW}$ ratios, based on figures published by Harmann,[5] were within normal limits (see Table II). The right side of the heart of D4 was dilated, and an area in the anterior aspect of the right ventricular wall was markedly thinned. The tricuspid valve was fenestrated and incompetent, and was very edematous when examined histologically. Microscopically, the thinned area in the anterior aspect of the right ventricle showed only replacement of the myocardium by fat cells, with no fibrosis or cellular reaction and no occluded vessels.

In a papillary muscle of the left ventricle of D6 a small area of fibrosis was found, and on the mitral valve a fresh verrucous lesion, containing colonies of staphylococci, was noted. In D8 there was a small calcified lesion in a papillary muscle of the left ventricle. No recent infarctions or occlusions of the coronary arteries could be found in any of the hearts (see Table II). On microscopic examination, rarely a small artery showed slight thickening of the media, but not more than was found in the control hearts.

Lungs.—Passive congestion was noted in D2 and D4.

Liver.—The liver of D4 was contracted, hard, and nodular, resembling cardiac cirrhosis. That of D2 showed acute passive congestion, and that of D6, chronic passive congestion.

Pancreas.—Agonal dilatation of the arterioles, with fresh petechiae, was found throughout the pancreas of D1 and D2.

Spleen.—A few of the spleens contained abnormal amounts of pigment deposits.

Kidneys.—Except for both kidneys of D6, which were the seat of extensive acute and chronic suppurative nephritis, only an occasional area of infarction was found.

Intestinal Tract.—The mucosa of the stomach was essentially negative. In all the dogs there were shallow depressions, measuring from 1 to 3 cm. in diameter, which extended from the pylorus to the appendix, were covered with epithelium, and varied in number from six to twenty per animal. On histologic examination, none of them had the characteristics of a peptic ulcer; they were composed of markedly thinned mucosa overlying collections of lymphoid cells. The mucosa of the intestine of the two dogs which had died during an injection was beefy red from an inch beyond the pylorus to the rectum; that of the other dogs was a purplish pink.

Adrenal Gland.—Nothing abnormal was observed.

Arterial Tree.—No atheromata or occlusions were found in the aorta or its branches as far as they could be traced.

DISCUSSION

An attempt to produce myocardial degeneration with injections of acetylcholine was unsuccessful, even though each dog was given the maximum dose it could tolerate. In addition, to avoid the possibility of any decomposition of the acetylcholine before it reached the blood stream of the animal, the crystals were added directly to the normal saline just before each injection. Cardiac murmurs were heard in only two of the animals. Cardiac disability developed in one dog, and was evidently caused by tricuspid insufficiency resulting from healed endocarditis. Two acute deaths took place, probably because of ventricular fibrillation; post-mortem examination of these hearts was entirely negative. The electrocardiograms, for the most part, remained normal, and the P-R interval was not prolonged in any instance. (Hall noted that the P-R interval increased to 0.4 second in one case.) There was no histologic evidence of vascular changes and myocardial lesions, for sections from control animals showed comparable changes.

Inasmuch as Hall, et al., have stated that, with a daily dose of 50 mg. of acetylcholine, they noted the appearance of cardiac murmurs after 9 to 136 consecutive injections, and death as a result of cardiac failure after 21 to 227 injections in six out of eight dogs, it was felt that their method had been given a fair trial. The fact that, in the study

here reported, a rest period of four months was given to the animals does not render the results invalid because the production of myocardial disease should be an accumulative process.

Gilbert and LeRoy,[6] in substantiation, have closely adhered to the method employed by Hall, et al., using first a dose of 50 mg., but later increasing it to 100 mg., of acetylcholine daily, and have given daily injections totaling 606, 558, 546, 531, 510, 458, and 430 mg., respectively, to seven dogs without producing more than a minor degree of myocardial and coronary artery damage. None of their animals developed signs of cardiac failure or significant electrocardiographic changes, although they noted the appearance of systolic murmurs in some of them.

CONCLUSIONS

Intravenous injections of acetylcholine hydrobromide were given over a ninety-minute period, six days a week, for a total of 101, 100, 100, 100, 91, 90, 60, and 60 mg., respectively, to eight dogs. Following a subsequent rest period of four months, six of the dogs received additional injections numbering 4, 56, 89, 125, 126, and 127, for a final total of 227, 216, 190, 186, 156, 100, 94, and 60 injections, respectively. The daily dose, which averaged from 150 to 445 mg., was increased from 50 mg. to as high as 1,100 mg., depending on the degree of tolerance to the drug manifested by the individual animal. Two of the dogs developed cardiac murmurs, one after twelve injections, the other after forty-six injections; both were pregnant at the time, and one of them had a bacterial endocarditis involving the tricuspid valve. Two dogs died while being injected, probably from ventricular fibrillation. The electrocardiograms and morphologic changes in all the hearts were comparable to those of the control dogs.

An attempt to produce severe coronary artery damage and myocardial failure in dogs by intravenous acetylcholine injections was unsuccessful.

I wish to thank Dr. Nathan Rudo for interpreting the pathologic data.

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DEPROTEINATED PANCREATIC EXTRACT (DEPROPANEX)

II. Effect of Intravenous Administration in Rabbits*

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IN UTILIZING any therapeutic agent, the most efficacious method of administration is naturally desired. In the use of pancreatic extracts, intravenous administration has been associated with unfavorable reactions in the past. N. W. Barker and R. W. Graham[1] stated that when pancreatic extracts were injected intravenously into animals, toxic effects were noted. J. B. Wolffe,[2] similarly, has warned against the intravenous administration of these extracts. However, with the development of deproteinated pancreatic extract, which is practically protein-free, as well as free of insulin, histamine, and acetylcholine, the possibility of intravenous administration was considered more favorably. The present study was instituted in order to note the effects of large amounts of deproteinated pancreatic extract when administered intravenously to rabbits.

METHODS AND MATERIALS

Twelve rabbits which weighed from four to eight pounds, were approximately five months old, and were all males except one, were used. Three of this group were anesthetized by intraperitoneal injections of sodium amytal (60 milligrams per kilogram of body weight). The nine others were unanesthetized. The rabbits were bound down to a rabbit board, and deproteinated pancreatic extract was administered by intravenous infusion to seven rabbits and by a multiple syringe method to five. The routine intravenous infusion drip apparatus was used for the slow method, and a multiple syringe for the rapid method. The time of administration was noted, and the onset of the rabbits' reactions were charted in the order of their occurrence. Two animals, used as controls, received saline by the intravenous infusion method. Electrocardiograms were taken before and after the administration of deproteinated pancreatic extract in several rabbits. Six rabbits were given deproteinated pancreatic extract by intravenous infusion at a rate of 1.1 to 1.5 c.c. per minute (Group I, see Table I). One rabbit was given deproteinated pancreatic extract by the multiple syringe method at a rate of 1.7 c.c. per minute, and four received the extract by the same method at a rate of 3 to 8 c.c. per minute (Group II).

RESULTS

No signs were noted after the administration of the first 5 to 10 c.c. of deproteinated pancreatic extract intravenously. Salivation usually occurred after the animal had received 15 c.c. The subsequent signs,

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TABLE I

TOXICITY OF DEPROTEINATED PANCREATIC EXTRACT INJECTED INTRAVENOUSLY IN RABBITS

RABBIT NO.	SEX	WEIGHT KG.	DEPROTEINATED PANCREATIC EXTRACT				METHOD
			TOTAL AMOUNT C.C.	C.C. PER KG. BODY WEIGHT	TOTAL INJECTION TIME MIN.	RATE C.C. PER MIN.	
Group I							
1003	M	2.2	290	131.8	255	1.1	Infusion
1006	M	2.7	260	96.3	205	1.2	Infusion*
1002	M	2.0	153	76.5	102	1.5	Infusion Anesthetized
1001	M	2.0	100	50.0	101	1.0	Infusion*
1005	M	1.8	87	48.3	60	1.4	Infusion
43	M	2.0	73	36.5	60	1.2	Infusion
2	M	2.4	100	41.7	60	1.7	Syringe Anesthetized
Group II							
46	M	2.0	38	19.0	13	3.0	Syringe
568	M	3.6	48	13.3	15	3.2	Syringe Anesthetized
6	F	3.2	55	17.2	7	8.0	Syringe
4	M	3.0	54	18.0	6	9.0	Syringe Anesthetized
Controls							
1007	M	2.4	250 c.c. saline	104.2	60	4.0	Infusion*
1006	M	2.7	200 c.c. saline	74.1	70	2.8	Infusion*

*Animal survived.

mostly parasympathomimetic, occurred at variable intervals of administration. Among the prominent manifestations, in the order of their occurrence, were lacrimation, rhinorrhea, increased muscle tone to tremors, increased peristalsis to diarrhea, involuntary micturition, rapid respiration, rapid pulse to irregular pulse, generalized convulsions, and, terminally, pulmonary edema.

There was no difference in the onset of signs in those animals which were anesthetized as compared to those which were unanesthetized.

At the rate of 1.1 to 1.5 c.c. per minute (Group I), from 73 c.c. to 290 c.c. of deproteinated pancreatic extract were given by the intravenous infusion method. From 36.5 to 131.8 c.c. per kilogram of body weight were received by this group.

The one rabbit which received the extract at the rate of 1.7 c.c. per minute by the multiple syringe method tolerated 100 c.c. in sixty minutes, or 41.7 c.c. per kilogram of body weight. When the rate of administration was increased from 3 to 8 c.c. per minute (Group II), doses from 38 to 55 c.c. were sufficient to cause death; an average of 16.8 c.c. per kilogram of body weight was given to this group.

The two saline controls survived the infusions. One received 250 c.c. at a rate of 4 c.c. per minute, and the other 200 c.c. at a rate

of 2.8 c.c. per minute. The only signs noted were evanescent tremors. One of these rabbits, No. 1006, was subsequently submitted to an infusion of deproteinated pancreatic extract and tolerated 260 c.c. of the extract without succumbing.

Rabbit No. 1001 survived 100 c.c. of deproteinated pancreatic extract, when the experiment was terminated. Thus these figures could have been higher had the rabbits been allowed to receive more deproteinated pancreatic extract. No delayed reaction or latent effects were noted in these animals which survived. Electrocardiograms revealed no significant changes, but, because the series was small, no definite evaluations can be made.

DISCUSSION

From this study, it seems apparent that further investigations in the direction of intravenous administration might be worth while. No untoward reactions in man were noted in giving over 1,000 injections of this substance intramuscularly in the hip, in doses of 3 c.c. three times a week. We have previously reported its use, intravenously, in twenty patients without severe systemic reactions. Because protein is practically absent from this preparation, danger from this component of earlier extracts is eliminated. Since rabbits weigh only one thirty-fifth as much as adult human beings, and can tolerate massive doses per kilogram of body weight, further investigative work, using slow intravenous administration of small doses of deproteinated pancreatic extract in man, can be instituted without great risk. It is only by studying a large group of patients, over a long period of time, that conclusions can be drawn as to the relative value of this substance in the treatment of peripheral vascular disease.

CONCLUSIONS

1. Deproteinated pancreatic extract is a relatively nontoxic substance when injected intravenously into rabbits.

2. The slower the administration of the extract, the greater the tolerance of the animal to still larger doses.

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A COMPARISON OF LEADS IV R AND IV F

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CHEST leads were first used clinically by Wolferth and Wood,[1] in 1932. Within a few years precordial leads came into widespread use. Following this there developed confusion because of lack of uniformity in nomenclature and technique. In 1938 a report of the Committee for the Standardization of Precordial Leads appeared,[2] and a few months later the Committee published further recommendations in a supplementary report.[3] Of all the chest leads considered, Leads IV R* and IV F† were advised for ordinary purposes. Furthermore, the Committee expressed preference for Lead IV F, but suggested that more investigation of the apical leads would be necessary before final judgment.

Following the suggestions of the Committee, many workers investigated the relative values of the two apical leads. Edwards and Vander Veer,[4] using the six standard positions in CR, CL, and CF, in addition to Leads IV R and IV F, concluded that Lead IV R was the one of choice provided the heart is not appreciably enlarged. (In the latter event the precordial electrode is never to be placed farther to the left than the anterior axillary line.) Likewise, Wood and Selzer,[5] in a study of Leads IV R and IV F and several other chest leads, came to the conclusion that the right arm site for the indifferent electrode was most informative, and advised its routine use in preference to the left leg. Geiger[6] is of the opposite opinion. He found significant discrepancies between Leads IV R and IV F in sixty-four out of 400 records. In fifty-five of these records the diagnostic abnormalities were more marked in IV F, and in only nine were they more marked in IV R. He concluded that Lead IV F was distinctly better than Lead IV R.

Shortly after the publication of the Committee's recommendations,[2, 3] we began to take both apical leads routinely, in addition to the standard limb leads. In view of the diversity of opinions we have compared Leads IV R and IV F in our cases.

METHOD

Eight hundred seven electrocardiograms were made on 389 patients. These included the standard limb leads and Leads IV R and IV F. The number of records on each patient ranged from one to fourteen. The patients were all adults who had been sent to the laboratory because they were known to have, or were suspected of having, heart disease. Beyond this no selection of patients or electrocardiograms was made.

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*Indifferent electrode on the right arm; exploring electrode over the apex.

†Indifferent electrode on the left leg; exploring electrode over the apex.

The position of the subjects varied from recumbent to sitting at slightly less than 90 degrees. All records were taken on a Cambridge "Hindle" electrocardiograph. The patient's resistance was in all instances 2,000 ohms or less. The galvanometer connections were made in such a way that relative positivity of the precordial electrode was represented by an upward deflection.[2] The interpretation of each electrocardiogram was made upon consideration of all the leads taken.

ANALYSIS

The purpose of our study was to ascertain whether one of the apical leads was *significantly* more diagnostic than the other. To accomplish this we have classified Leads IV R and IV F in relation to each other as "similar" and "dissimilar." If both were normal or both were abnormal they were considered similar; on the other hand, if one was normal and the other was abnormal they were considered dissimilar. An apical lead was termed abnormal if (a) the initial positive deflection was absent, or 2 mm. or less in height;[7, 8] (b) the S-T junction was elevated more than 2 mm. or depressed more than 1 mm.;[9] (c) the T wave was other than upright[9, 10] or was upright and less than 1 mm. in amplitude.[9, 11, 12*]

The similar records comprised a large number (767) of IV R and IV F leads, so that a brief description of the general characteristics of their complexes may be a valuable addition to the already available information concerning them. Forty dissimilar records were found among the 807 records compared in the above manner, and these will be analyzed separately.

ELECTROCARDIOGRAMS IN WHICH LEADS IV R AND IV F WERE SIMILAR

P Waves.—The P waves in 715 records were compared; several records were omitted because of the presence of auricular fibrillation. In Lead IV R the P wave was a positive deflection in 694 (97 per cent), and a negative deflection in 5 (0.69 per cent). It was isoelectric in five (0.69 per cent), and of more than one phase in eleven (1.52 per cent). Of the positive deflections, only thirty-two were less than 1 mm. in amplitude. Thus slightly more than 95 per cent of the positive P waves were 1 mm. or more in size, and 92.5 per cent of all P waves in IV R were both positive and at least 1 mm. in amplitude. The maximum amplitude was 4 mm.

In Lead IV F the P wave was positive in 266 (37.2 per cent), isoelectric in 209 (29.2 per cent), and negative in 191 (26.7 per cent). It was of more than one phase in forty-nine (6.84 per cent). Of the positive deflections, only seventy-three (27.4 per cent) were 1 mm. or more in height. Thus only 10.2 per cent of all P waves in this lead were both positive and at least 1 mm. in amplitude. The maximum amplitude was 2 mm.

*The references cited above give varying figures for the minimum amplitude of T in Leads IV R and IV F. A minimum of 1 mm. was chosen arbitrarily, after consideration of these figures, as most representative.

In the 715 cases, P in IV F was similar to P in IV R in ten (1.39 per cent), and P in IV R was exceeded in size by P in IV F in ten (1.39 per cent). The P wave in Lead IV R was therefore more often positive and more often larger than P in Lead IV F. Furthermore, P in IV R was usually positive and easily measured, whereas P in IV F was isoelectric, or so small a positive or negative deflection that its identification was difficult.

QRS Complexes.—A few records were omitted because large R or S waves extended beyond the edge of the record. Seven hundred twelve complexes were analyzed. Of these, the algebraic summation of the complexes in both IV R and IV F were in the same direction in 615 (86.4 per cent), and in different directions in ninety-seven (13.6 per cent). In this latter group of ninety-seven tracings, QRS in IV R was positive in eighty, and QRS in IV F was positive in the remaining seventeen.

The amplitude of QRS was calculated in the 615 cases in which the direction was the same. The complexes were considered to be of equal amplitude if the algebraic summations were within 2 mm. of each other. With this classification, QRS of IV R and IV F were equal in 165 (26.8 per cent). The QRS of IV R was larger than that of IV F (2.5-27 mm.; average 7.46 mm.) in 340 (55.3 per cent) and the QRS of IV F was larger than that of IV R (2.5-22 mm.; average 5.41 mm.) in 110 (17.9 per cent). In all 712 cases, i.e., including those considered equal, QRS in IV R was larger than QRS in IV F (average 4.09 mm.).

S-T Junction.—In considering the S-T junctions of the electrocardiograms with similar apical leads, all records in which a digitalis effect was noted were omitted. Seven hundred seven records were studied. The junction was isoelectric in both leads in 338 records (47.8 per cent), and deviated equally (less than 1 mm. difference) in 265 (37.5 per cent). In fifty-two records (7.4 per cent) the deviation was more positive (2 mm. or more difference) in IV R, and the same held true in an equal number of cases for IV F.

In the last two groups (104 records) the deviation of the S-T junction was positive in both IV R and IV F in thirty-seven cases, in twenty-four of which IV R was more positive than IV F. In these groups the deviation was negative in both IV R and IV F in twenty-five cases, in sixteen of which IV R was more negative than IV F.

Thus it is seen that the S-T junction in Leads IV R and IV F was isoelectric in about half the cases, and deviated equally in about four-fifths of the remaining cases. When the junction deviated unequally (1 mm. or more difference) but in the same direction, the deviation, whether positive or negative, was more marked in IV R.

T Waves.—The T waves of the 754 records were analyzed. In 483 (63.9 per cent of the total), T was positive in both leads. Among these 483 in which T was positive in both, T in IV R was larger than T in IV F in 357 (73.9 per cent), and smaller in fifty-four (11.2 per cent). They

were equal in seventy-two (14.9 per cent). In 199 records, T was negative in both leads; it was of the same amplitude in thirty-seven (18.6 per cent), of greater negative amplitude in IV F in ninety-one (45.7 per cent), and of greater negative amplitude in IV R in seventy-one (35.7 per cent). There remained seventy-two records in which the T waves were neither both positive nor both negative. Among these seventy-two were twenty-one records of anterior and apical infarction in which Leads IV R and IV F were considered similar because both were diagnostic, but in which the T waves varied. In nineteen of these twenty-one records T in IV F was negative, whereas T in IV R was diphasic or of abnormally small positive voltage. The reverse held true in the remaining two records. In this same group of seventy-two there were ten records of posterior and basal infarction, among which T in IV F was more abnormal than T in IV R seven times, with the reverse holding true in the remaining three.

ELECTROCARDIOGRAMS IN WHICH LEADS IV R AND IV F WERE DISSIMILAR

In forty of the 807 records which were studied, Leads IV R and IV F differed significantly from each other. These differences were noted in cases of myocardial infarction, in records showing a digitalis effect, and in a miscellaneous group. The dissimilarities will be discussed under these headings.

MYOCARDIAL INFARCTION

Anterior Infarction.—In cases of anterior myocardial infarction, 209 records on sixty-five patients were available. Leads IV R and IV F differed in 3.8 per cent (eight records). In seven out of eight records Lead IV F was more diagnostic; the difference was confined to an inverted, diphasic, or small T wave in IV F, with a normal T in IV R. The abnormal T in IV F appeared earlier and lasted longer.

Posterior Infarction.—In cases of posterior myocardial infarction, 161 electrocardiograms on fifty-one patients were analyzed. Leads IV R and IV F differed in 6 per cent (ten) of the records. Diagnostic abnormalities were found in Lead IV R in six cases and in Lead IV F in four cases. The abnormalities were confined to (a) diphasic T waves; (b) abnormal depression of the S-T junction; (c) a combination of (a) and (b); and (d) inversion of the T wave. The diphasic T wave occurred in six of the ten records.

Miscellaneous Group.—This group includes thirty-one records on eight patients. Three patients were thought to have both anterior and posterior myocardial infarction, and three were thought to have infarction of the lateral wall of the left ventricle (proved in one case by postmortem examination). The seventh and eighth patients were thought to have myocardial infarction, but the infarcted area could not be localized, and the diagnosis itself was not definitely established. Four dis-

similar records in two cases were noted; the abnormalities occurred in Lead IV F. In two of five records from a patient with combined anterior and posterior myocardial infarction, Lead IV R was normal but Lead IV F showed abnormal depression of the S-T junction. In two of five records from a patient with questionable infarction the standard leads and Lead IV R were normal, but T in IV F was of abnormally low amplitude.

DIGITALIS EFFECT

A digitalis effect was noted in fifty-three records on thirty-nine patients. In forty-eight of the fifty-three, changes of the S-T junction or the T wave were sufficiently alike in both leads to be considered similar, but the changes were slightly more marked in Lead IV R in all forty-eight records. In the remaining five records (9.4 per cent) Lead IV F was normal, and Lead IV R alone indicated the effect of digitalis.

MISCELLANEOUS GROUP

Lead IV F Abnormal.—Of fourteen records on six patients with various types of disease, nine showed an abnormal Lead IV F but a normal IV R. The abnormalities were confined to the T wave, which was either diphasic (six instances), inverted (two instances), or isoelectric (one instance). The abnormal T wave appeared earlier in IV F than in IV R in a patient with bronchopneumonia, and lasted longer in a patient with pulmonary embolism. Abnormal changes were noted in three cases of angina pectoris, but the records were not exactly comparable because one patient had hypertension, another had normal blood pressure, and the third had had a Beck cardiac anastomosis two years before.

Lead IV R Abnormal.—Of twelve records on four patients with various types of disease, four showed an abnormal Lead IV R but a normal IV F. In one of several records taken on two patients with hypertension, Lead IV F was normal, whereas in Lead IV R the S-T junction was depressed and the T wave inverted in one case, and the T wave diphasic in the other. In a case of hemopericardium the expected elevation of the S-T junction was diagnostically more marked in Lead IV R. In a patient, aged 29 years, with a history of streptococcus infection of the throat seven years previously and subsequent paroxysmal tachycardia, Lead IV F was normal but T in IV R was markedly inverted.

COMMENT

Leads IV R and IV F differed significantly from each other in only a small percentage (5 per cent) of cases. These differences were not found consistently in any one lead in any given group of electrocardiograms, save in those showing a digitalis effect, in which records Lead IV R was distinctly superior. In the other groups the abnormalities were unevenly divided.

Lead IV F had a numerical superiority of twenty-four to sixteen in relation to the dissimilar electrocardiograms, but a superiority of only seventeen to fourteen in relation to the number of patients these records represented. There was agreement between Lead IV R and IV F in 95 per cent of the 807 records. Significant variations from normal were observed in Lead IV F and not in Lead IV R in an additional 3 per cent (twenty-four records), whereas in 2 per cent (sixteen records) the significant variations from normal were observed only in Lead IV R.

SUMMARY OF ALL RECORDS

1. Eight hundred seven electrocardiograms, with the standard leads and Lead IV R and IV F, were analyzed with a view to comparing the two apical leads.

2. Using the criteria described above, Leads IV R and IV F were found to be dissimilar (significantly different) in forty records (4.9 per cent).

3. In the 767 records in which Leads IV R and IV F were similar, the P wave, the QRS complex, and the T wave were larger and more positive, on the whole, in Lead IV R than in Lead IV F.

4. In anterior myocardial infarction with dissimilar apical leads (3.8 per cent), Lead IV F was diagnostic earlier and longer (seven out of eight records).

5. In posterior myocardial infarction with dissimilar apical leads (6 per cent), Lead IV R was the abnormal lead in six out of ten records.

6. In one doubtful and one unusual type of myocardial infarction, Lead IV F was abnormal in all of four dissimilar records.

7. A digitalis effect was always more marked in Lead IV R, and in five cases was the only one of the two apical leads to display it.

8. In a miscellaneous group comprising thirteen dissimilar records, Lead IV F was the abnormal lead in nine records, and Lead IV R in four records.

9. In the great majority of all the dissimilar records the changes were confined to abnormalities of the T wave.

10. Of the forty dissimilar electrocardiograms, the abnormalities were noted in Lead IV F in twenty-four (3 per cent of total) and in Lead IV R in sixteen (2 per cent of total). In relation to the number of patients with dissimilar records, Lead IV F was abnormal in only seventeen cases, and Lead IV R in fourteen cases.

CONCLUSIONS

1. The use of both Leads IV R and IV F results in slightly greater accuracy than the use of either lead alone.

2. If only one apical lead is to be employed, either Lead IV R or Lead IV F may be used to the exclusion of the other without appreciable prejudice to the best electrocardiographic diagnosis.

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Department of Reviews and Abstracts

Selected Abstracts

Corcoran, A. C., and Page, Irvine H.: Arterial Hypertension. Correlation of Clinical and Experimental Observations. J. A. M. A. **116:** 690, 1941.

Angiotonin, or renin plus activator, when injected into animals produces those effects which have been shown to characterize arterial hypertension in man; namely cardiac augmentation, arteriolar constriction, and constriction of the efferent arterioles of the kidneys. This suggests the possibility that angiotonin is involved in the pathogenesis of essential and malignant hypertension in man.

The endocrine system, notably the adrenal cortex and hypophysis, appears to participate indirectly in that its secretions maintain the blood vessels and heart in a state receptive to hypertensive stimuli. The nervous system may play a similar part, especially in some types of hypertension in man in which the high state of nervous organization may even make it a prepotent factor.

The clinical picture and course of each case of hypertension is therefore probably a composite of the degree and kind of renal, endocrine, and nervous participation.

AUTHORS.

Christian, Henry A.: Earlier Diagnosis of Subacute Streptococcus Viridans Endocarditis. J. A. M. A. **116:** 1048, 1941.

Since patients with subacute *Streptococcus viridans* endocarditis so often come to the hospital without a diagnosis or with a wrong diagnosis, it is apparent that relatively few practitioners are aware of the usual early clinical picture of this disease.

The chief early symptoms in the 150 patients I have examined resulted from toxemia. They were complaints indicative of (a) malaise and fever in 52.6 per cent of cases at onset and 71.3 per cent at onset and in the early days of the disease; (b) joint or muscle pains in 42 per cent at or near onset; and (c) nauseas or loss of appetite in 16 per cent at onset and in the early days of the disease.

If these symptoms appear in a patient known or found to have evidence of chronic valvular or congenital disease of the heart and persist for more than one week without the development of evidence of other definite disease, the probability of bacterial endocarditis is great.

If in these patients embolic phenomena appear or a blood culture is positive, a definite diagnosis of bacterial endocarditis should be made.

If the condition referred to in either of the foregoing two paragraphs occurs, appropriate chemotherapy should be begun at once.

AUTHOR.

Brown, Clark E., and Richter, Ina M.: Medial Coronary Sclerosis in Infancy. Arch. Path. **31:** 449, 1941.

A case of coronary calcification in infancy is reported with data on six additional cases abstracted from the literature. This type of vascular change is part of general arterial calcification, the chief site of which appears to be the internal elastica.

Coexistent intimal proliferations are noted frequently. These may result at times in occlusion. The cause of the lesion is in doubt, although some alteration in the calcium and phosphorus metabolism is suspected.

AUTHORS.

Meiks, L. T.: The Influence of Tonsillectomy on the Progress of Rheumatic Heart Disease. J. Indiana M. A. **33**: 666, 1940.

The present study is based on 200 patients who present definite evidence of rheumatic heart disease. Of this group of 200 cases thirty-one had had tonsillectomies before the development of any manifestation of rheumatic fever. In the remaining 169 patients admitted to the hospital after development of definite rheumatic heart disease, tonsillectomies were done eventually on seventy-nine. Of these seventy-nine patients operated upon, there were twenty-eight in whom there were valid indications. In twenty-three patients tonsillectomies were done upon questionable indications. In twenty-eight patients tonsillectomies were done only because of the presence of rheumatic heart disease. The author traces statistically the course of these 79 patients. He offers the following conclusions.

The removal of tonsils and adenoids usually does not modify the course of rheumatic heart disease, and the presence of this condition is not of itself an indication for their removal.

In the presence of definite local indication for tonsillectomy and adenoidectomy in a patient with rheumatic heart disease, it is proper that the operation be done.

The operation, as a rule, should not be done in the presence of signs of activity of the rheumatic infection.

There is occasionally an immediate recrudescence of rheumatic activity after tonsillectomy and adenoidectomy.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. IV. Influence of Season and Certain Meteorological Conditions. Pub. Health Rep. **55**: 1809, 1940.

A review of the literature indicates that in Great Britain rheumatic fever and chorea occur with greatest frequency in the fall and during December and least often in the spring and early summer. The experience of most American writers suggests that in this country these conditions are most common during the late summer and fall.

In agreement with this consensus this study indicates that in Philadelphia admissions involving rheumatic fever and chorea are most frequent in the spring and least frequent in the fall. The greatest number of admissions involving rheumatic fever was in April, the fewest in October. The peak of admissions involving chorea occurred in May; the smallest number in November.

Despite the fact that admissions involving rheumatic fever occurred with greatest frequency during the first six months of the year, especially the spring, and least often during the fall, considerable variations were noted from year to year. In a study of only five years' duration, the greatest number of admissions occurred twice during April, twice during May, and once during June.

Seasonal variations of chorea were not as great as of rheumatic fever. The seasonal distribution of these conditions was only roughly comparable. There was apparently no relationship between the number of patients for these diseases.

Admissions involving these conditions did not occur with greatest frequency during the coldest months or with least frequency during the warmest months. After allowing for the possibility that several weeks had elapsed between onset and admission to hospital, it is doubtful whether the onset of the greatest number of cases

of rheumatic fever and chorea coincides with the coldest time of the year. These diseases are apparently no more common during years with low mean temperatures or following severely cold winters. Prolonged cold of winter, rather than severe cold or the onset of cold weather, seems more likely to be responsible for the increased frequency of rheumatic fever and chorea during the spring. It is difficult to dissociate the role of prolonged cold from lack of sunshine.

No relationship was indicated between the amount of precipitation and the number of patients with rheumatic fever and Sydenham's chorea.

Although admission of patients with rheumatic heart disease is more common during the spring and least frequent during the fall, seasonal variations are not as great as for rheumatic fever and chorea.

Seasonal variations of deaths from rheumatic heart disease are not as great as admissions involving rheumatic fever, chorea, or rheumatic heart disease but are somewhat greater than for deaths from all heart disease and deaths from all causes.

The seasonal distribution of the admission of patients with rheumatic conditions and of deaths from rheumatic heart disease is dissimilar in many respects to the distribution of deaths from acute coronary occlusion.

In contradistinction to strictly rheumatic conditions, practically no seasonal variations were noted in admissions or deaths from subacute bacterial endocarditis regardless of its relationship to rheumatic heart disease.

AUTHOR.

Hedley, O. F.: Rheumatic Heart Disease in Philadelphia Hospitals. V. Distribution by Locality of Rheumatic Conditions in Philadelphia. Pub. Health Rep. **55**: 1845, 1940.

A review of the literature indicates a considerable lack of agreement concerning the roles of proximity to watercourses and dampness due to low altitude in the causation of rheumatic fever and chorea. The consensus of most investigations suggests that these diseases are distinctly more prevalent in areas occupied by the underprivileged than the better-to-do.

Rheumatic fever, Sydenham's chorea, and nonfatal and fatal rheumatic heart disease among hospital patients in Philadelphia tended to occur with greatest frequency in the sections of the city occupied to a large extent by the poor. This relationship was not, however, invariable. Some of the city wards in which the rentals were the lowest and the density of population the greatest did not have the greatest number of hospital admissions or deaths per 100,000 population. A low rate of admissions and deaths was noted in every city ward inhabited for the most part by persons living under reasonably favorable economic circumstances. This is doubtless due in no small measure to the fact that persons in the better-to-do economic brackets do not regularly seek admission to hospitals for the treatment of medical conditions. It is difficult to escape the impression that the conditions under study occur with the greatest frequency in sections of the city occupied by poverty-stricken persons.

These diseases tended to occur with greatest frequency in the eastern half of South Philadelphia and in a section of the midcity near the Delaware River.

These studies do not suggest that proximity to a watercourse is an important factor. The distribution of low rentals corresponded more closely to the Delaware River water front than the distribution of rheumatic fever and chorea.

Relatively low rates of admissions and deaths in hospitals from these diseases were indicated in a number of city wards occupied largely by colored persons.

The distribution of Sydenham's chorea is roughly comparable to rheumatic fever, except that a somewhat more general distribution is indicated. It is even less common than rheumatic fever in city wards largely occupied by negroes.

A more general distribution was indicated in mortality from rheumatic heart disease in hospitals than of admissions for rheumatic fever, Sydenham's chorea, and rheumatic heart disease. This suggests that the more acute or fulminating forms of rheumatic infection occur with relatively greater frequency among the extremely poor. An analogy is noted between tuberculosis and rheumatic infection.

AUTHOR.

Hines, Edgar A., Jr., and Lander, Howard H.: Factors Contributing to the Development of Hypertension in Patients Suffering From Renal Disease. J. A. M. A. **116**: 1050, 1941.

The results of this study show that in a series of 264 patients who had various types of urologic diseases, those patients who had a high normal blood pressure on their visit were four to five times as likely to have hypertension subsequently as were those who had a low normal blood pressure, regardless of the type or extent of the urologic or renal lesion and regardless of whether the onset of symptoms of the disease of the urinary tract occurred before or after the original blood pressure reading. In respect to the correlation between the original blood pressure and the subsequent development of hypertension, there was little difference between the series of patients suffering from urologic disease and a control series of persons who had no renal or urologic disease. Furthermore, as far as could be determined on the basis of a study of the family histories of our patients, heredity plays a similar role in the development of hypertension associated with renal disease and, in many instances, of essential hypertension. We do not interpret our data as constituting a denial that renal disease may have been a contributing factor to the development of hypertension in some of our patients. However, these data do seem to cast some doubt on the importance of renal disease in producing hypertension in the series as a whole and call attention to the importance of exercising caution in attributing a role of primary importance to a renal lesion simply because it is found in a patient who has hypertension. This study demonstrates that factors concerning the control of blood pressure which are inherent in each person may be of similar importance in the development of hypertension when there is an associated renal disease as in the development of hypertension when no renal disease is present. The presence or absence of these inherent factors may explain why hypertension develops in some patients who have a certain type of renal disease, whereas in other patients who have a similar type and extent of renal disease, hypertension does not develop.

AUTHORS.

Holman, Emile: Clinical and Experimental Observations on Arteriovenous Fistulae. Ann. Surg. **112**: 840, 1940.

In the first 24 to 48 hours after the establishment of a large arteriovenous fistula, the heart diminishes in size, and is followed, if the animal survives, by a prompt return to normal, and, subsequently, by a gradual dilatation which may be apparent within 4 to 5 days.

Death due to an excessive diversion of blood through the fistula may occur, accompanied by a marked diminution in cardiac size.

The dilatation that accompanies an arteriovenous fistula is not restricted to the heart but affects the vessels involved in the fistulous circuit. The same cause is responsible for both dilatations, an increase in the volume or bulk of blood flowing through that part of the circulatory system through which the blood short-circuited by the fistula must flow; namely, all the chambers of the heart, the proximal artery, the fistula, and the proximal vein.

In the growing animal the dilatation and enlargement may be very great without evidence of decompensation and may be accompanied by pronounced hypertrophy. It is suggested that when dilatation outstrips hypertrophy, decompensation occurs; when dilatation is paralleled by a commensurate hypertrophy, great enlargement and dilatation of the heart may occur without decompensation.

In a crucial experiment involving three litter mates of equal weight and stature, one acting as control, one having an aorta vena cava fistula 12 mm. in circumference, and one having an aorta vena cava fistula 18 mm. in circumference, there occurred an increase in blood volume commensurate with the size of the fistula.

In the same animals an increase in the capacity of the circulatory system occurred also commensurate with the size of the fistula. The increase in capacity and the increase in blood volume closely paralleled each other.

In an animal with bilateral femoral fistulae the increase in blood pressure and reduction in pulse rate were greatest when both fistulae were closed simultaneously and considerably less when either fistula was closed separately. The physiologic effect of a fistula, therefore, clearly depends upon the volume of blood diverted through the fistula and, consequently, upon its size.

The transient high systolic and diastolic pressures that persist for several days following operative closure of a fistula are due to the increase in blood volume that has occurred during the existence of the fistula. The permanent elevation of diastolic pressure is secondary to the elimination of an area of decreased peripheral resistance.

In animals having bilateral femoral fistulae, vena-caval pressures were highest with both fistulae open, least with both fistulae closed, and intermediate pressures were obtained on closing one or the other fistula separately. Venous pressures proximal to a fistula are determined by the volume of blood diverted through the fistula and, therefore, by the size of the fistula.

AUTHOR.

Bigger, I. A.: The Surgical Treatment of Aneurysm of the Abdominal Aorta. Ann. Surg. **112:** 879, 1940.

An attempt has been made to collect the cases of aneurysm of the abdominal aorta and common iliac arteries treated by operations (excluding wiring) upon the aorta. The various surgical procedures which may be applicable to these aneurysms (excluding wiring) are discussed.

Two new cases are reported:

One patient, a poor surgical risk, developed left-sided heart failure with pulmonary edema and died following occlusion of the aorta proximal to the aneurysm.

A young man with a ruptured traumatic aneurysm had a preliminary occlusion of the aorta proximal to the aneurysm and one month later a restorative endoaneurysmorrhaphy. When examined one year after the endoaneurysmorrhaphy, the patient appeared to be well; there was no evidence of aneurysm, and the lumen of the aorta was obviously patent.

We realize that there is a marked difference between traumatic and spontaneous aneurysms and that the methods of treatment used in one may not be applicable in the other. For example, it is unlikely that one would find a spontaneous aortic aneurysm suitable for the type of operation, reconstructive endoaneurysmorrhaphy, used in our second case, but it seems likely that a small number of spontaneous aneurysms will be found suitable for obliterative endoaneurysmorrhaphy. Such operations probably should not be attempted unless the aneurysm arises distal to the renal arteries and, almost certainly, should not be attempted when the aorta is diffusely calcified. Proximal occlusion of the aorta should be undertaken as a pre-

liminary operation. This brings about shrinkage of the sac so that at the second operation either the aorta or the common iliac arteries may be ligated immediately distal to the aneurysm.

If the iliac arteries are permanently occluded, care should be taken to see that the ligatures are placed on the common iliacs, not the external iliacs, and the internal iliacs (hypogastrics) should be carefully protected because of their great importance as collateral channels.

Also, all vessels communicating with the sac should be ligated insofar as possible before the sac is opened. Only by the employment of meticulous preliminary preparation can one hope for success in such cases.

Aneurysms of the proximal portion of the abdominal aorta which have such essential arteries as the celiac, superior mesenteric, or both renals arising from the sac, probably should not be treated surgically, while in those aneurysms arising above the renal arteries but without any of the essential arteries originating from the sac proximal ligation may be justifiable.

AUTHOR.

Elkin, Daniel C.: Aneurysm of the Abdominal Aorta. Ann. Surg. **112**: 895, 1940.

This report is concerned primarily with the effects of ligation of the abdominal aorta and consideration of those cases in which this procedure has been carried out. Therefore, the treatment of aortic aneurysm by other methods has not been considered. In only six patients upon whom ligation has been performed may the procedure be considered in any degree successful. Other means of treating an aneurysm of this vessel should be considered, but it is improbable that wiring, coagulation, or the application of the Matas principle of endoaneurysmorrhaphy could be carried out with any great hope of success. The effect upon the heart and circulation should be further studied, and methods of producing occlusion by other means than ligation must be developed before the operation can be successfully performed in the majority of cases.

AUTHOR.

Pearse, Herman E.: Experimental Studies on the Gradual Occlusion of Large Arteries. Ann. Surg. **112**: 923, 1940.

Closure of the aorta both by intravascular thrombosis and by extravascular irritation has been demonstrated. It remains to perfect the methods by which this is done, for they can, in all probability, be improved.

AUTHOR.

Gage, Mims, and Ochsner, Alton: The Prevention of Ischemic Gangrene Following Surgical Operations Upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics. Ann. Surg. **112**: 938, 1940.

We have employed the physiologic method, i.e., sympathetic block, of increasing the collateral circulation as a preliminary procedure to the ligation of major peripheral arteries in ten cases. In all but two of these cases, the collateral circulation was found to be inadequate by the Matas compressor test. In the other two cases, one of which was an aneurysm of the common iliac and the other a stab wound of the common femoral, the test could not be applied. Of these ten cases, one was a mycotic aneurysm of the right common iliac artery. Following sympathetic block and ligation of the common iliac at its origin, there was no change in color and no decrease in temperature of the corresponding extremity. There were two cases of arterial aneurysm of the femoral artery and three cases of popliteal aneurysm which

were cured by obliterative endoaneurysmorrhaphy. Three of the cases consisted of arteriovenous aneurysm, two of which were femoral and one of which was popliteal. These are treated by quadruple ligation. There was one case of stab wound of the common femoral which required ligation. In none of these cases of ligation of the major peripheral arteries treated by preliminary sympathetic block was there any evidence of ischemia or deficiency of the peripheral circulation.

We have also used sympathetic block in four cases of embolus of the femoral artery. In one case the embolus was removed after sympathetic block. The other three cases were not operated upon. In all these cases the classic clinical manifestations of arterial embolism were present. Following novocain block of the lumbar sympathetic ganglia and chain on the affected side, there was a loss of numbness and a return to normal of color and temperature of the extremity. In peripheral arterial embolism there is not only high incidence of ischemic gangrene, but also a high mortality, the gangrene increasing the mortality. Therefore, we believe that sympathetic block will not only materially decrease the incidence of ischemic gangrene but will also lower the immediate mortality.

AUTHORS.

Heinbecker, Peter: A Role for Surgeons in the Problem of Essential Hypertension. Ann. Surg. **112**: 1101, 1940.

Essential hypertension results when there is narrowing of peripheral arterioles with a maintained cardiac output. The vascular narrowing, presumably, is effected by a renal pressor substance released during a state of renal asphyxia.

It is believed that the initiation of the renal arteriolar narrowing necessary to bring about the renal asphyxia may be effected by nervous or humoral influences.

Regardless of the manner of its initiation, the process can become self-perpetuating. Neither nervous nor endocrine influences need, thereafter, play an essential role.

It is regarded as highly probable that hypertension occurs particularly in persons whose blood vessels are so constituted that they respond hyperdynamically to vasopressor influences. If such pressor influences are present in abnormal amounts, even normal renal blood vessels may constrict sufficiently to initiate renal ischemia.

Experimental and clinical evidence is cited to show that continued functional narrowing of blood vessels leads to occlusive narrowing. The degenerative changes characteristic of the occlusive disease are presumed to follow interference with the function of the vasa vasorum.

Splanchnic section may be expected to relieve renal ischemia initiated by vasoconstrictor influences if the renal ischemia has not become self-perpetuating.

Evidence that epinephrine lowers the threshold for excitatory influences on the nervous system and increases the magnitude of the cortical response to identical peripheral stimuli is presented.

The symptomatic relief afforded by splanchnic section, in cases where there is no drop in blood pressure, is considered due to adrenal denervation.

Experimental evidence that a substance produced as a consequence of renal ischemia may increase in certain animals the tone of the smooth muscle of the iris and nictitating membrane is reported. Under such circumstances the effect of exogenous epinephrine on these structures is also enhanced.

Typical case records showing the effect of splanchnic section at various stages of hypertensive disease are presented.

A role for the surgeon in the solution of the problem of essential hypertension is to determine the number and types of cases in which nervous influences set into activity the mechanism by which hypertension is initiated. This can be done only if cases are treated in their initial stage.

AUTHOR.

Book Review

HYPERTENSION AND NEPHRITIS: By Arthur M. Fishberg, M.D., Associate in Medicine, Mt. Sinai Hospital, New York, Ed. 4, 1940, Lea and Febiger, Philadelphia, 779 pages, 41 illustrations, $7.50.

During the rather short period which has elapsed since the appearance of the previous edition of Dr. Fishberg's book, a very large volume of new knowledge has been added to the subject of hypertension. Since this new knowledge is critically surveyed in the new edition, it is practically a new book. The subject is surveyed in its broadest aspects, and is discussed fully from the viewpoint of vascular function. Comprehensive and up-to-date discussions of chemical, physiologic, and pathologic aspects of hypertension are included. The rapidly growing and extensive literature dealing with recent experimental work is critically examined and admirably summarized. However, the purely practical phases of hypertension and nephritis are not neglected, but are maintained at the previous standard of excellence, as presented in the earlier editions.

Most books on clinical medicine tend to deal with the subject under discussion either from the standpoint of disease entities, or from the standpoint of symptoms. Dr. Fishberg uses both approaches. Beginning with a consideration of renal function, various manifestations of renal disease, such as uremia, edema, and albuminuria, are considered in painstaking detail. The several types of nephritis are then discussed in an unusually clear manner. The last portion of the book deals with hypertension, which is approached from all different points of view.

The more recent developments in these several fields have been thoroughly sifted by the author, and he has included references to most of the new work, as well as careful, critical summaries of the significance of such work. This difficult task in a field which is changing so rapidly has been performed in excellent fashion. Certainly no book in the English language can compare with this one in the field of hypertension and nephritis. Practicing physicians, medical students, and investigators will all join in hoping that Dr. Fishberg will continue to present from time to time new editions of his book, which is now generally accepted as a medical classic.

TINSLEY R. HARRISON.

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association stands alone as the national organization devoted to educational work relating to diseases of the heart. Its Board of Directors is composed of twenty-seven physicians representing every portion of the country.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning circulation of blood and lymph. Any physician or investigator in good standing may become a member of the section after election to the American Heart Association and payment of dues to that organization.

To coordinate and distribute pertinent information, a central office is maintained, and from it issues an ever widening stream of books, pamphlets, charts, posters, films, and slides. These activities all concern the recognition, prevention or treatment of the leading cause of death in the United States, diseases of the heart. The American Heart Journal is under the editorial supervision of the Association.

The income from membership and donations provides the sole support of the Association. Lack of adequate funds seriously hampers more widespread educational and research work imperative at this time. Great progress has been made, but much remains to be done.

Annual membership is $5.00 a year and journal membership at $11.00 includes a year's subscription (January-December) to the American Heart Journal and annual membership in this Association. A cordial invitation to join in this crusade is extended to you.

The American Heart Association solicits your support to the end that it may continue more effectively the campaign to which it has devoted all its energy.

**Executive Committee.*